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Aalto University
School of Science



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FINLANDS AKADEMI
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Brain networks: Why, what, how – and how not?

Onerva Korhonen

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31.5.2022

Slides: github.com/onerva-korhonen/presentations/blob/master/uppsala-310522.pdf

Networks: what and why?

(Repetitio est mater studiorum)

Network: a model of connections & interactions

- Internet, public transport, social networks

Tomás Saraceno: Algo-R(h)i(y)thm
(Photo: Milja Heikkinen)

Networks: what and why?

(Repetitio est mater studiorum)

Network: a model of connections & interactions

- Internet, public transport, social networks

Nodes: network's basic elements

- Web pages, stops, people

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Links: connections between nodes

- Web links, transport lines, social relationships

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- Weights?

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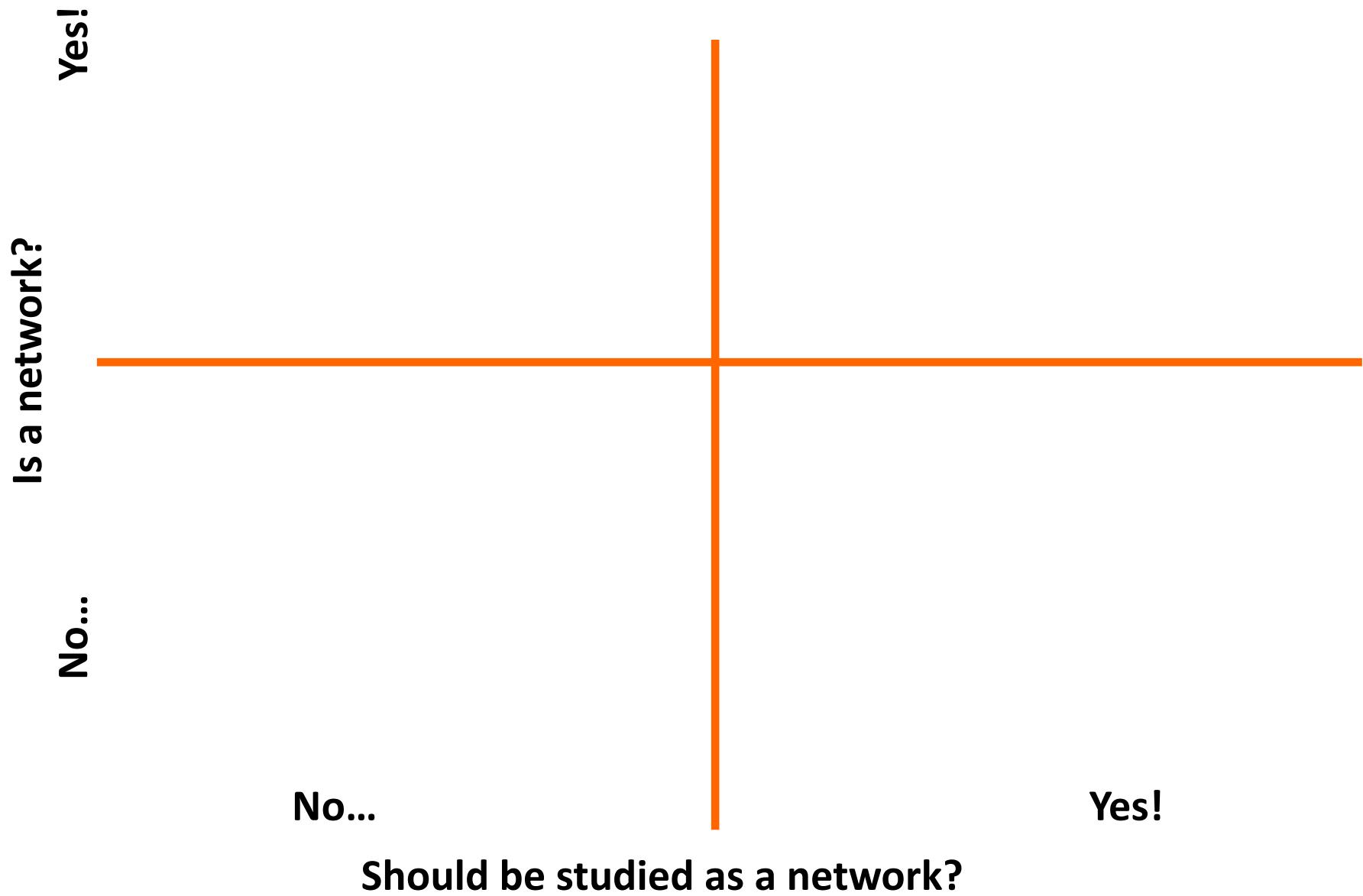
Nodes: network's basic elements

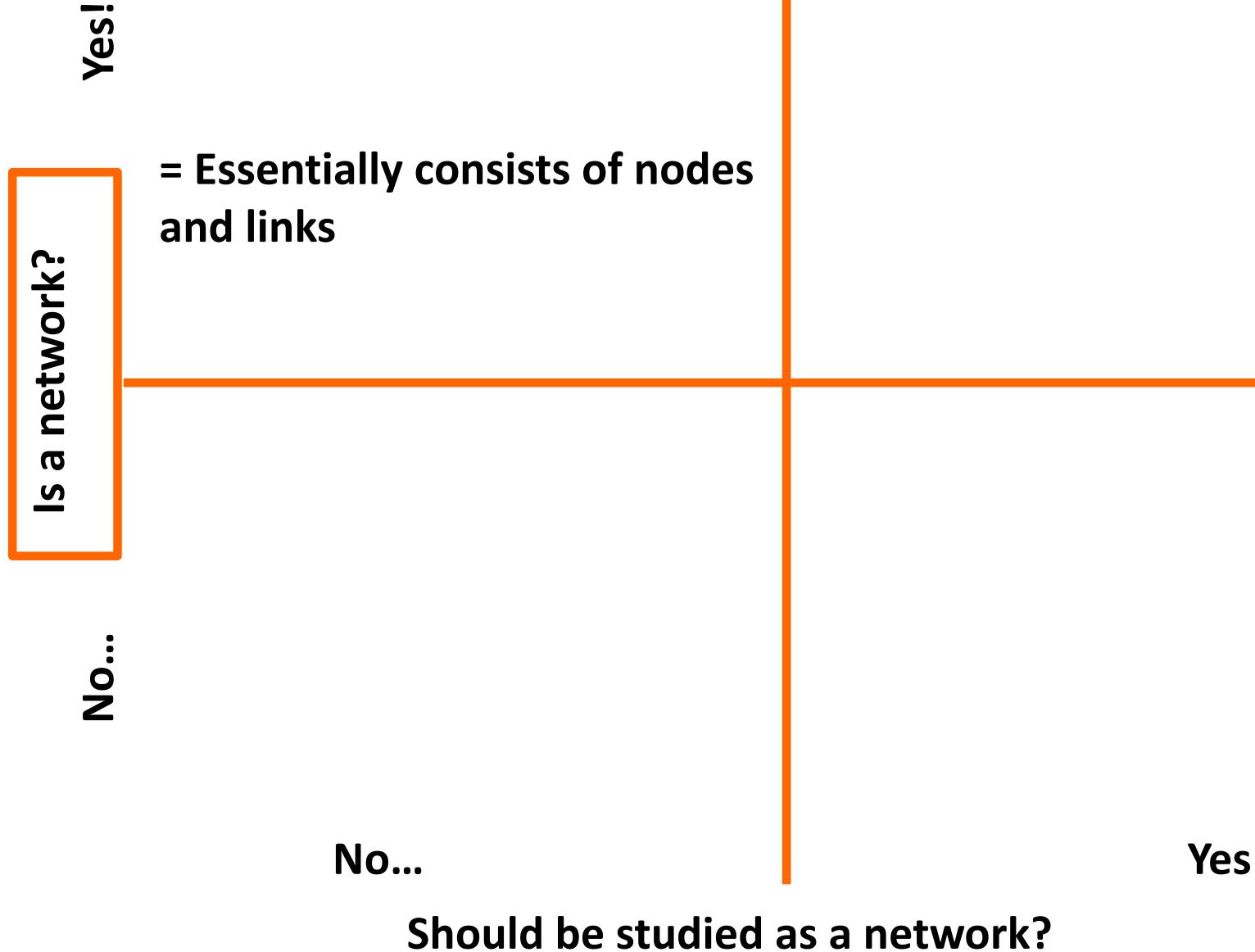
- Web pages, stops, people

Links: connections between nodes

- Web links, transport lines, social relationships
- Weights?
- Direction?

Not all that glitters is a network





Is a network?

Yes!

No...



= Network model gives new info,
increases understanding

No...

Yes!

Should be studied as a network?



Is a network?

No...

Yes!

No...

Should be studied as a network?

Yes!

ER model

WWW

Social relationships

Is a network?

No...

Yes!

No...

Should be studied as a network?

Yes!

Textual documents

Social relationships

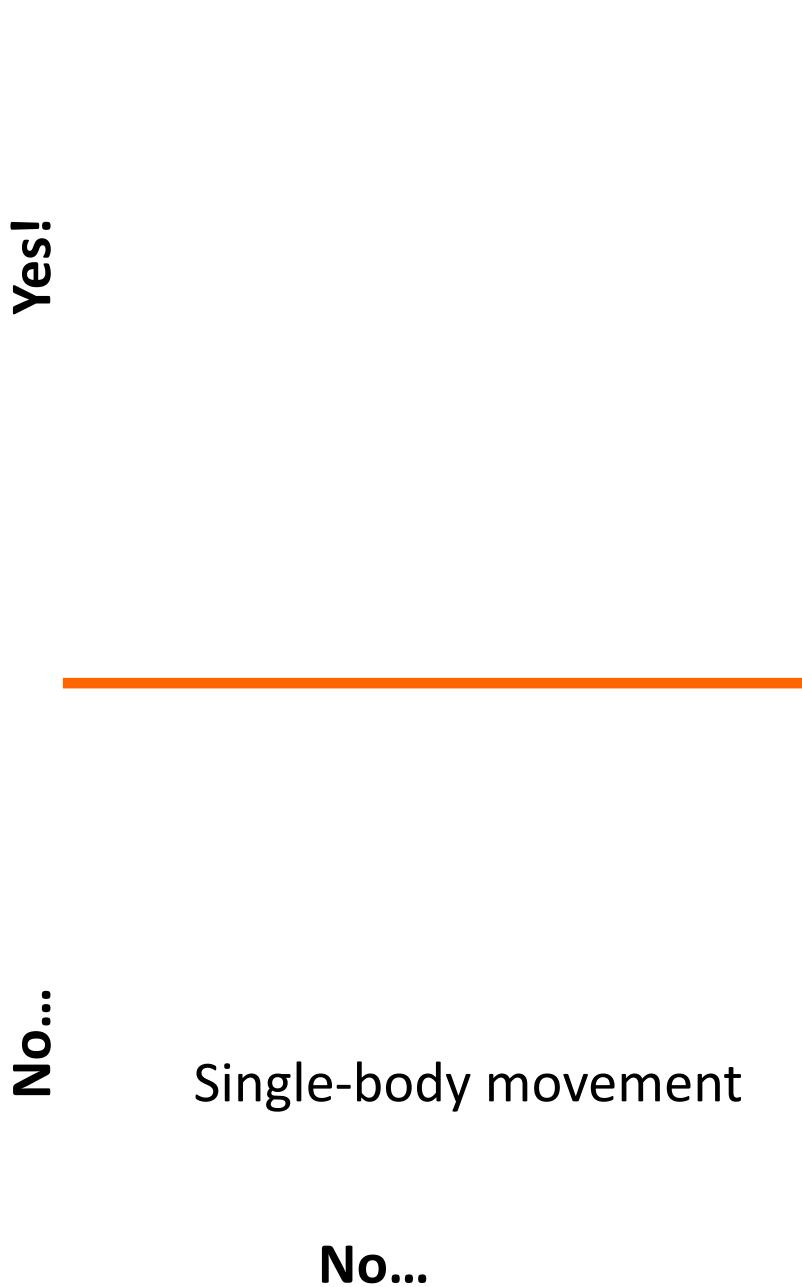
WWW

ER model

Is a network?

Yes!

No...



Should be studied as a network?

Single-body movement

Textual documents

No...

Yes!

WWW

Social relationships

ER model

Is a network?

Yes!

Multi-body movement

ER model

WWW

Social relationships

No...

Single-body movement

Textual documents

No...

Yes!

Should be studied as a network?

Is a network?

No...

Yes!

Single-body movement

Multi-body movement

No...

Yes!

Should be studied as a network?

Brain

???

???

???

WWW

Social relationships

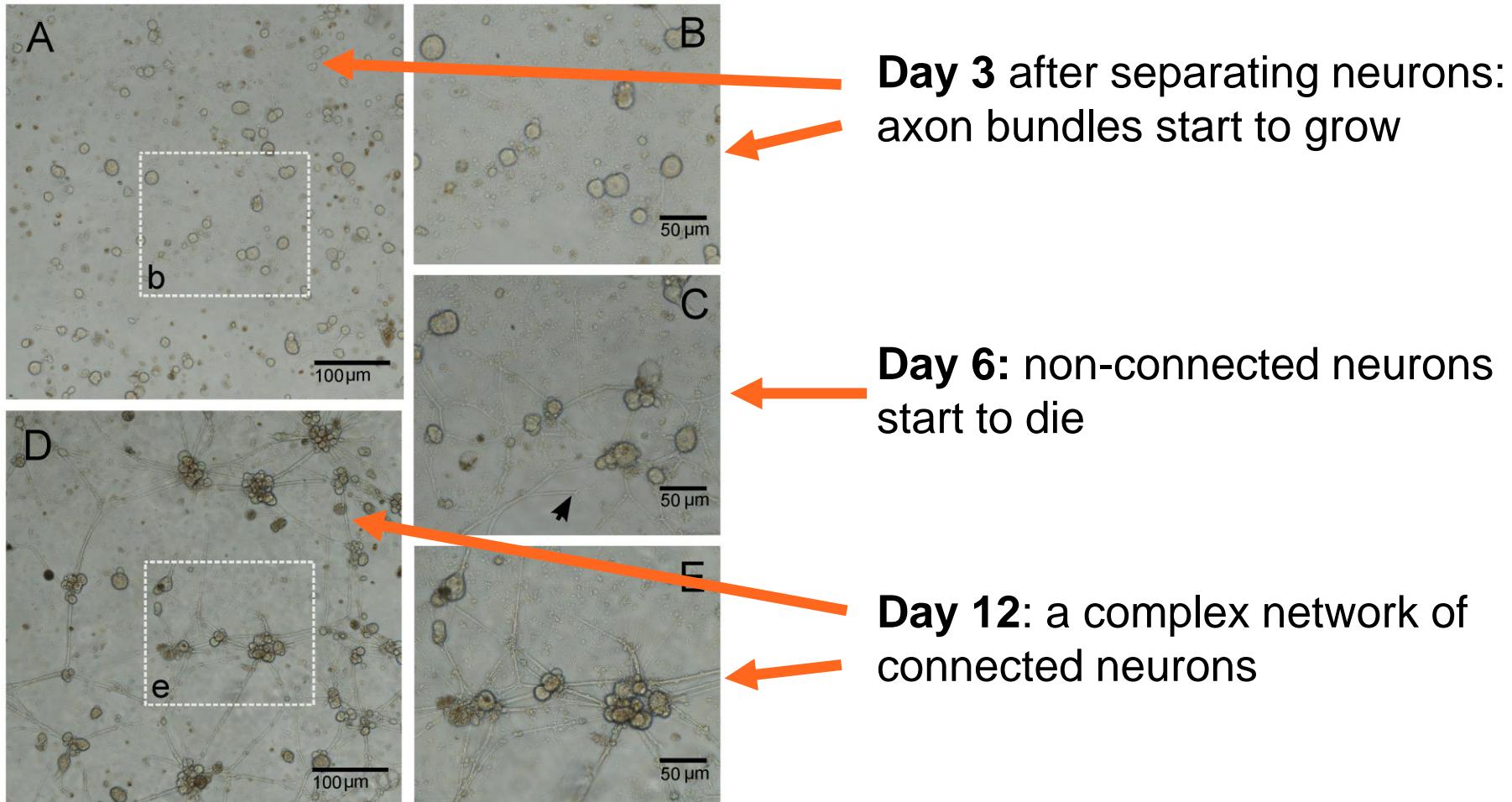
ER model

Textual documents

Brain networks: Why?

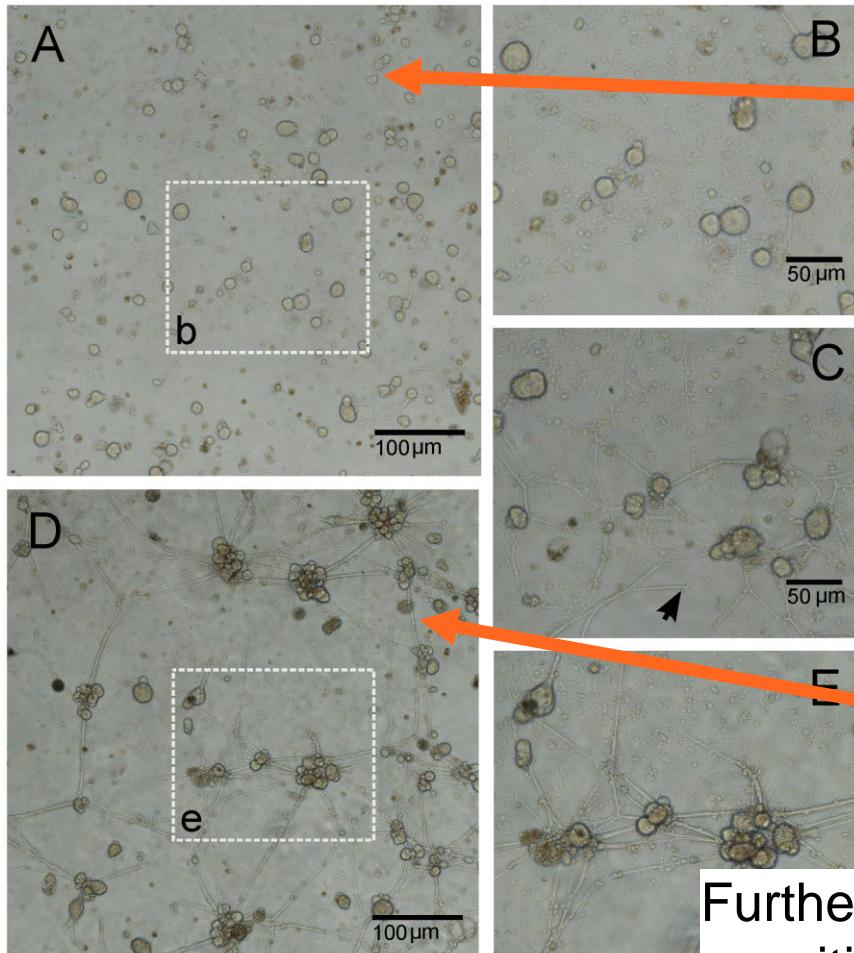
Why is the brain a network?

Brain: 10^{11} neurons, 10^{14} synapses



Why is the brain a network?

Brain: 10^{11} neurons, 10^{14} synapses



Day 3 after separating neurons:
axon bundles start to grow

Day 6: non-connected neurons
start to die

Day 12: a complex network of
connected neurons

Further evidence from functional neuroimaging:
cognitive tasks require co-activation of brain
areas

Brain networks: What?

Is a network?

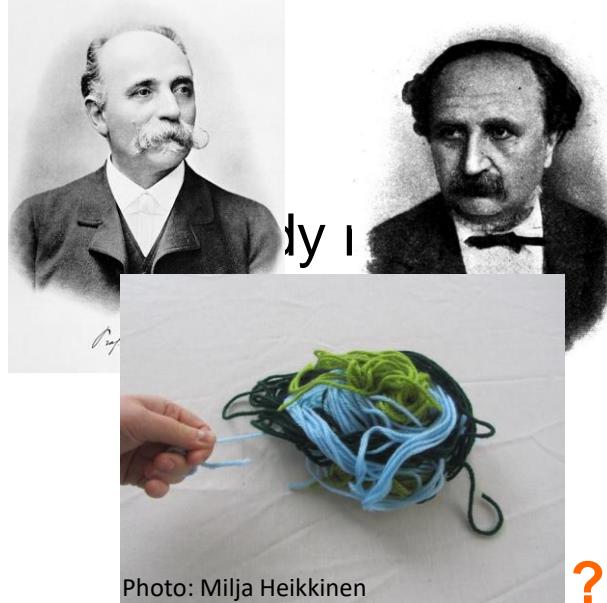
No...

Yes!

Single-body movement

No...

Yes!



Brain

???

???

WWW

Social
relationships

Textual documents

Should be studied as a network?

Figs: Wikimedia Commons, public domain

Yes!

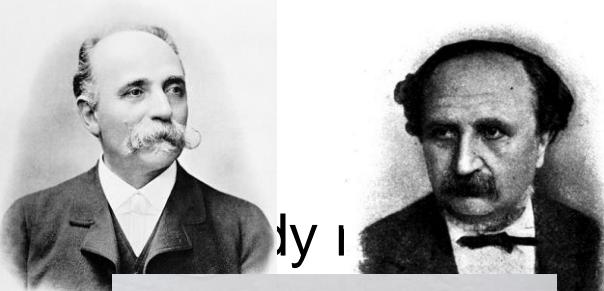
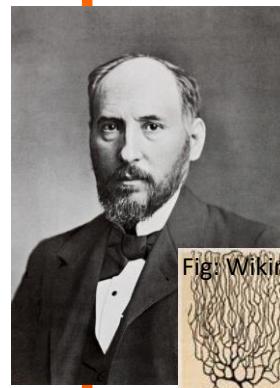


Photo: Milja Heikkinen

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Fig: Wikimedia Commons, public domain



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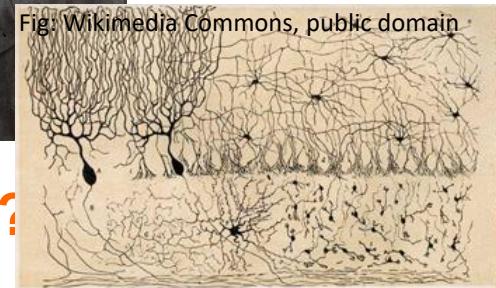


Fig: Wikimedia Commons, public domain

ER model

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onships

Brain

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Textual documents

Single-body movement

No...

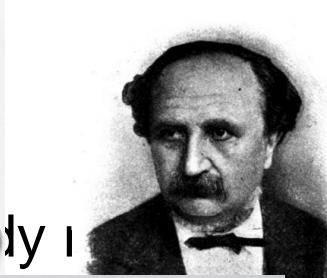
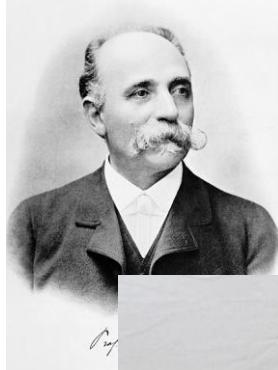
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Should be studied as a network?

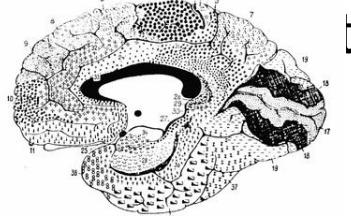
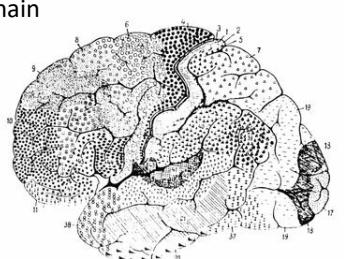
Is a network?

Yes!



???

Figs: Wikimedia Commons, public domain

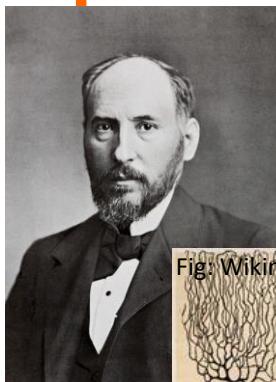


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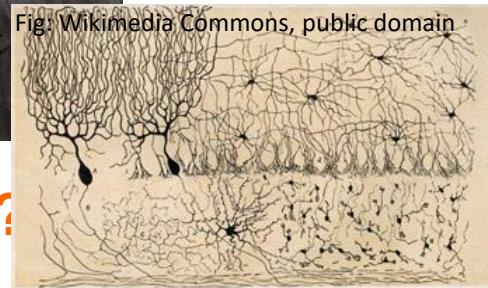
Brain

???

Figs: Wikimedia Commons, public domain



WWW



ER model

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Textual documents

Yes!

Should be studied as a network?

Figs: Wikimedia Commons, public domain

Is a network?

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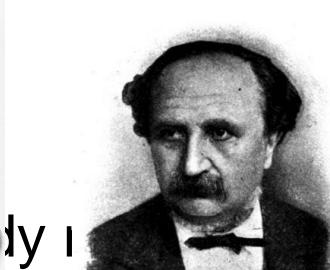


Photo: Milja Heikkinen

White et al. 1968: *C. elegans*

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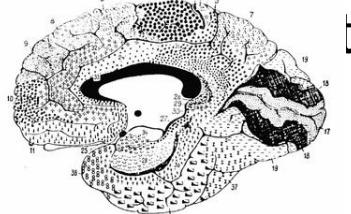
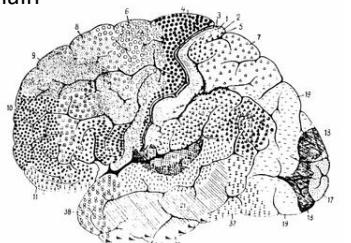
Brain

WWW



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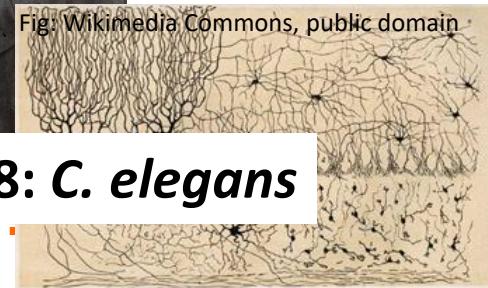
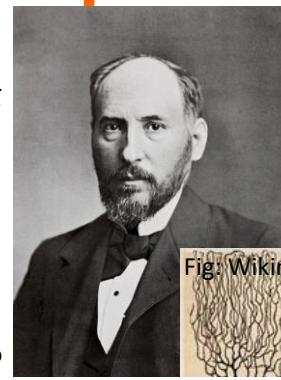
Textual documents



No..

Yes!

Fig: Wikimedia Commons, public domain



ER model

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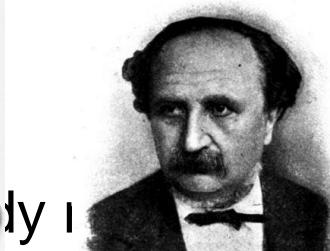
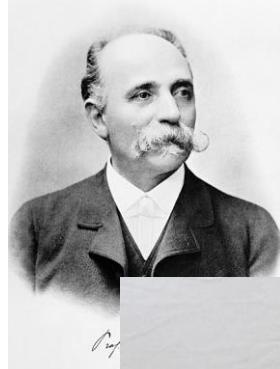


Photo: Milja Heikkinen

White et al. 1968: *C. elegans*

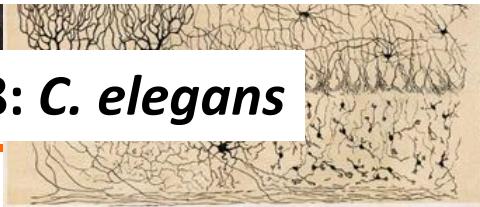
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Brain

Bassett & Muldoon 2016, Bassett & Sporns 2017: network neuroscience

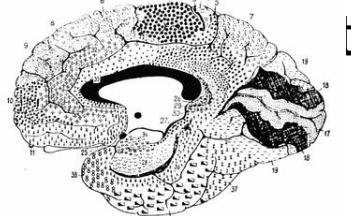
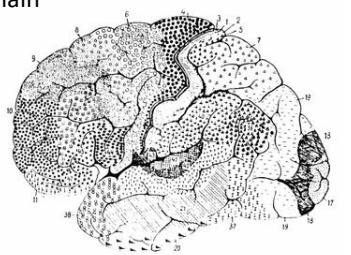


Sporns et al. 2005, Hagmann 2005: connectomics, connectome



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Textual documents



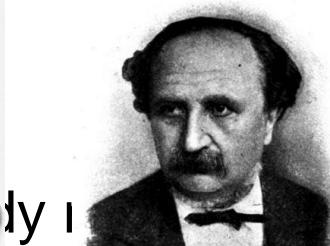
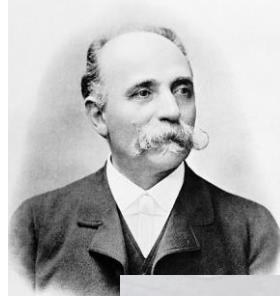
No..

Should be studied as a network?

Yes!

Is a network?

Yes!



White et al. 1968: *C. elegans*

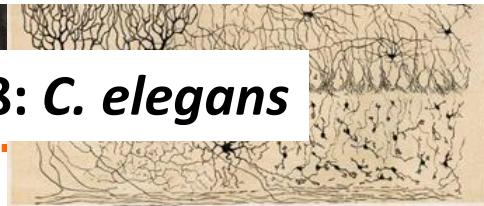
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Brain

Bassett & Muldoon 2016, Bassett & Sporns 2017: network neuroscience



Sporns et al. 2005, Hagmann 2005: connectomics, connectome



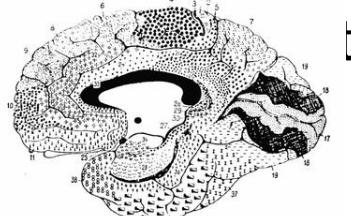
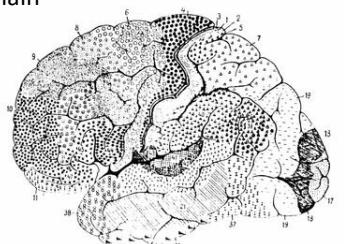
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how to define nodes/links? ↗S

structure/function? ↗S

correlation = causation?

Yes!



No..

Should be studied as a network?

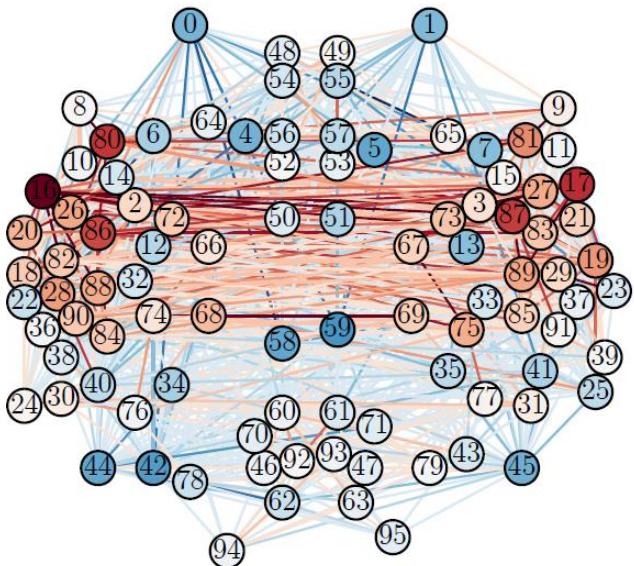
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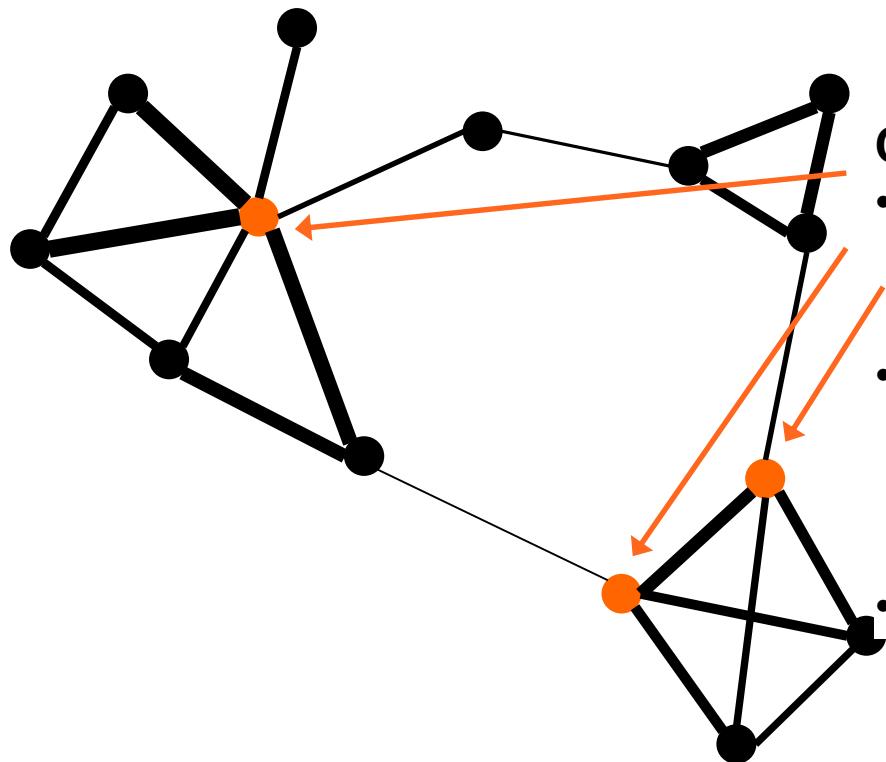
Network neuroscience

- 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:** anatomical connections
 - **Functional:** temporal coactivation
 - **Effective:** causality

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



How do func brain networks look like?

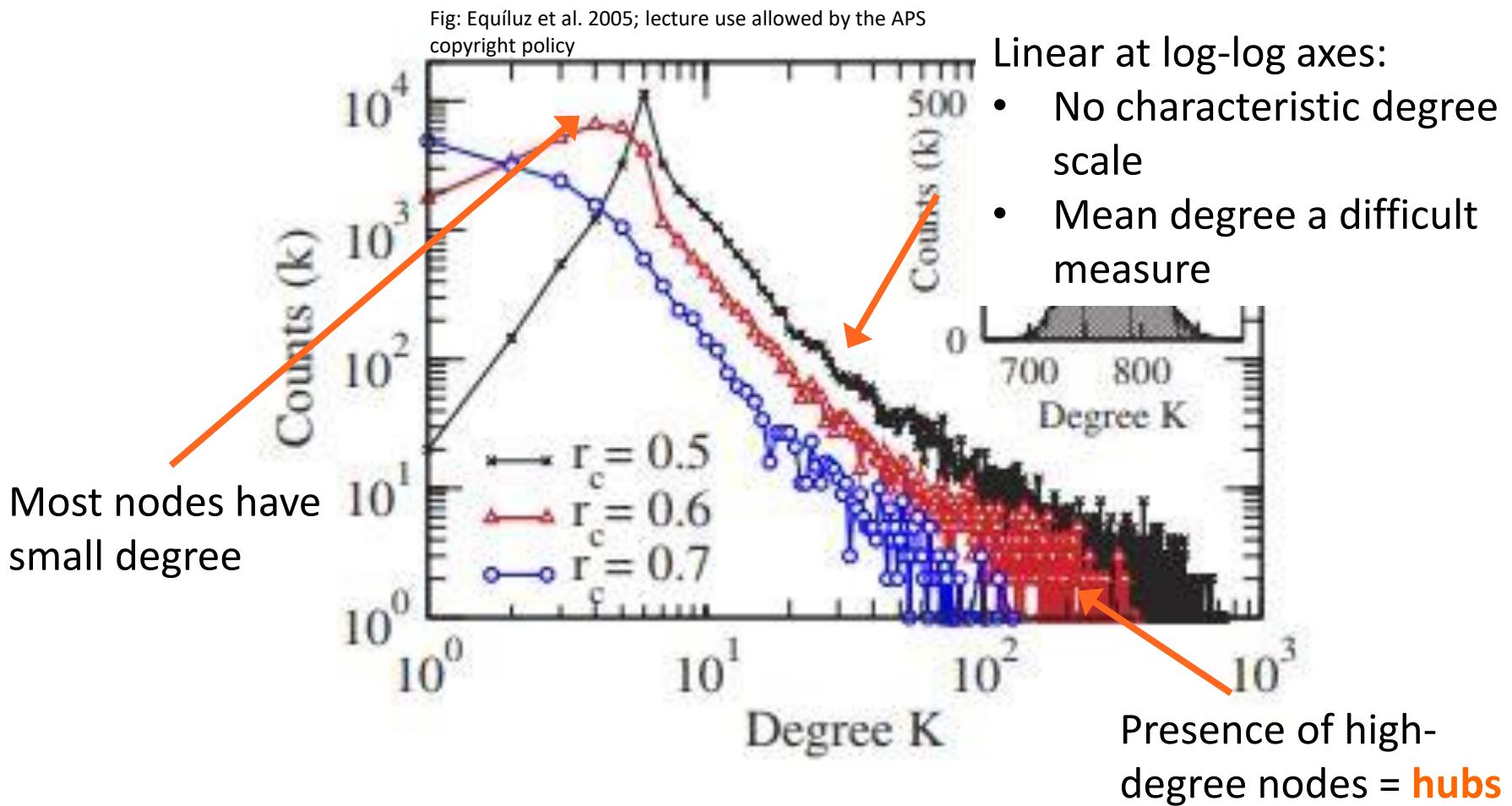


Centrality:

- Central nodes are "more important" in the network structure
- Most commonly used:
degree (= number of neighbours) and **strength** (= sum of weights)
Degree distribution

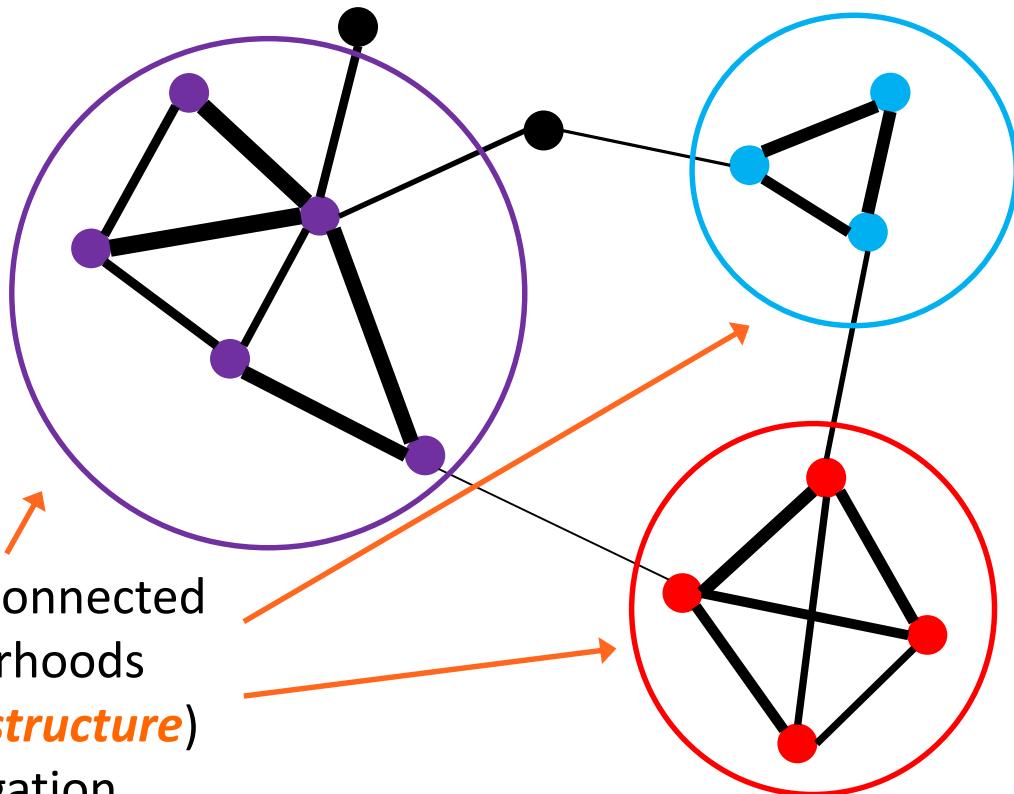
How do func brain networks look like?

Scale-freeness (Equíluz et al. 2005)



How do func brain networks look like?

Segregation-integration (Sporns 2013)

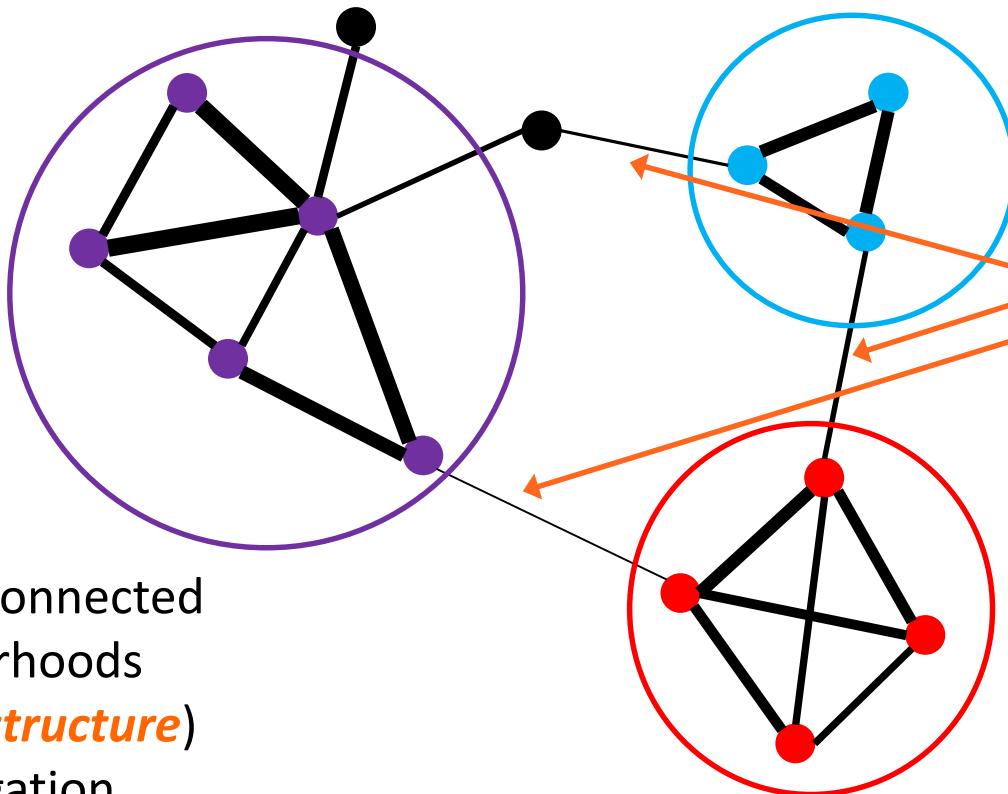


Strongly connected
neighbourhoods
(*module structure*)

- Segregation
- Functional specialization

How do func brain networks look like?

Segregation-integration (Sporns 2013)



Strongly connected
neighbourhoods
(**module structure**)

- Segregation
- Functional specialization

Weaker links between
modules

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

How do func brain networks look like?

Segregation-integration (Sporns 2013)

Most network links short
(= inside module)

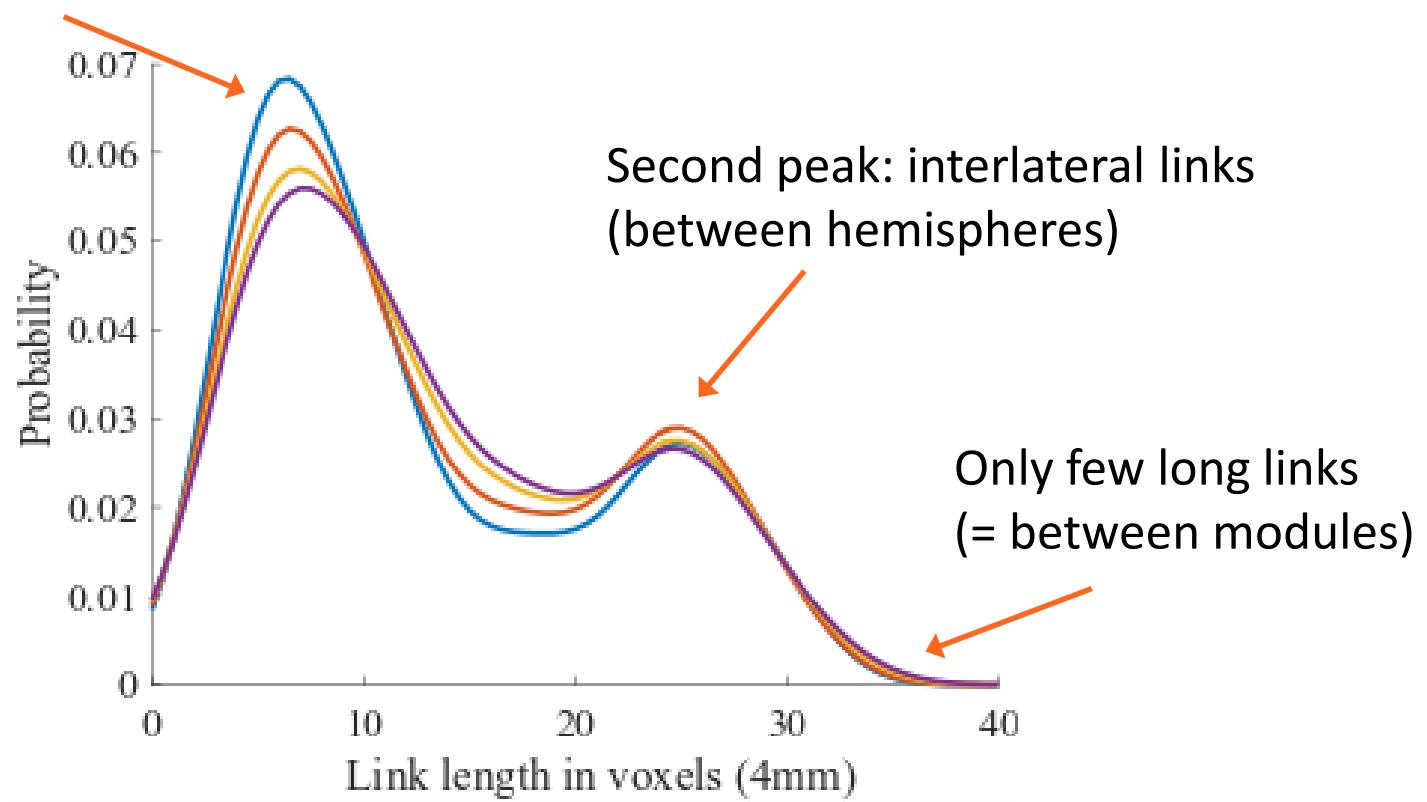


Fig: Alakörkkö et al. 2017.

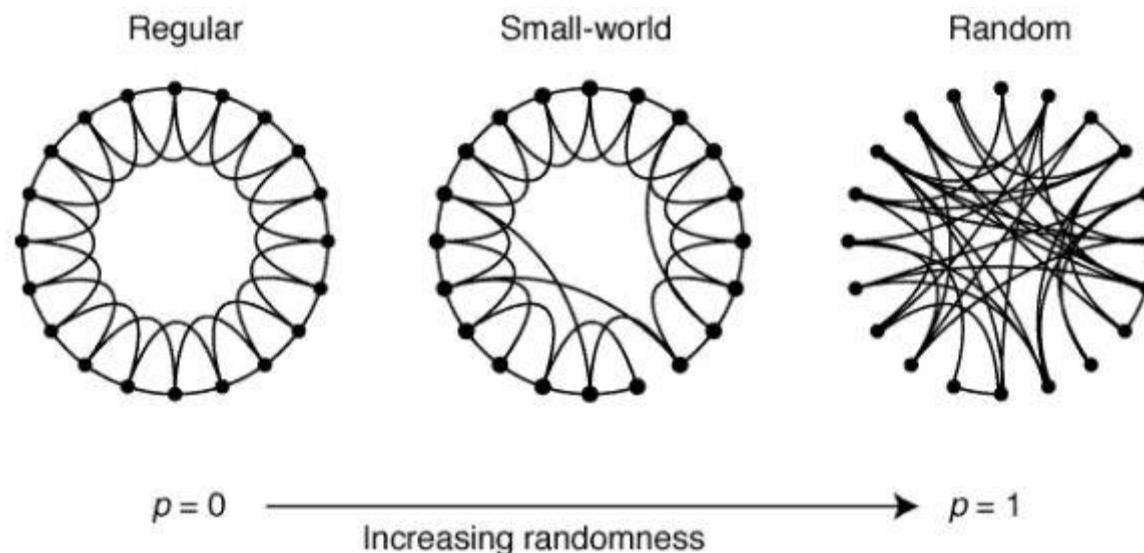
How do func brain networks look like?

Small-worldness

- For *C. elegans*: Watts & Strogatz 1998
- For structural nets: Sporns & Zwi 2004

Fig: Watts & Strogatz 1998

$$\sigma = \frac{C/C_{rand}}{L/L_{rand}}$$



Compared to random networks:

- High clustering ("friends of my friends are my friends")
- Similar shortest path length

How do func brain networks look like?

Small-worldness

- For *C. elegans*: Watts & Strogatz 1998
- For structural nets: Sporns & Zwi 2004

But is the brain really a small world? (Papo et al. 2016, Zalesky et al. 2012)

- Data collection and preprocessing?
- Measuring small-worldness? Null models?
- Interpretation?
- A fundamental organization principle or a consequence of limited space?

Increasing randomness

Compared to random networks:

- High clustering ("friends of my friends are my friends")
- Similar shortest path length

One never looks at the same network twice

Heraclitus, feat. O. Korhonen

Traditionally: static brain networks

- For func brain networks, correlations calculated over the whole time series

However, the brain needs to respond to changing stimuli

=> Natural assumption: brain networks change in time

Changes reported:

- Spontaneously over time, between tasks, with age, between health and disease
- In both links and nodes
- For review: Iraji et al. 2019, Korhonen et al. 2021 (section 3.4)

Brain networks: How?

Functional magnetic resonance imaging (= fMRI)

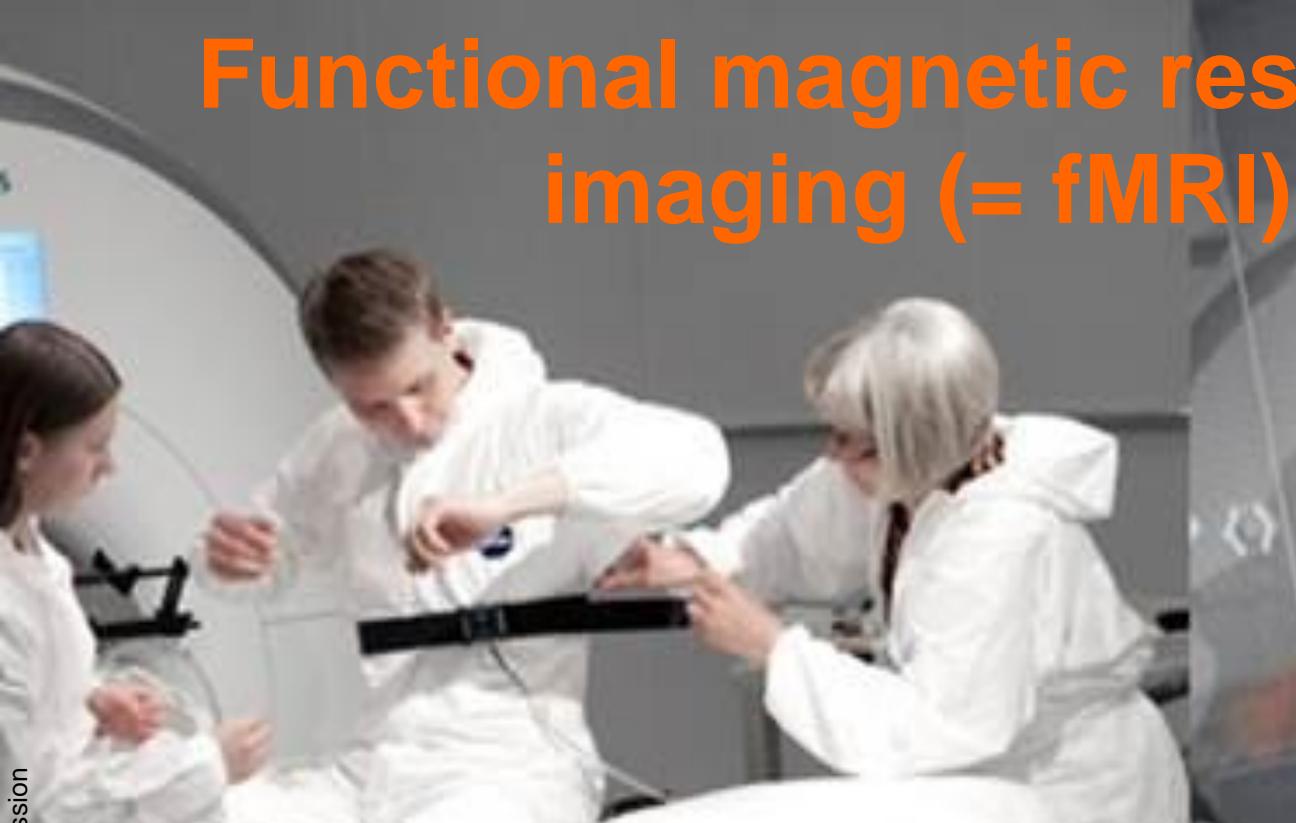
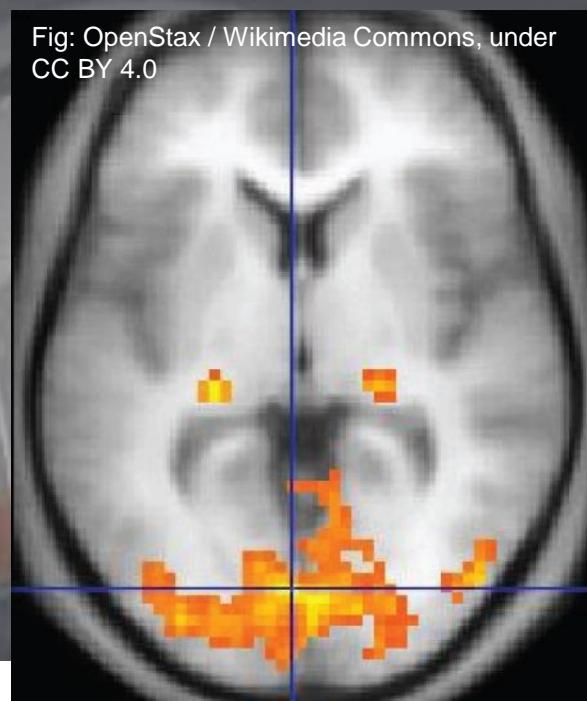


Fig: OpenStax / Wikimedia Commons, under CC BY 4.0



- Based on magnetic properties of haemoglobin
- Oxygen-rich and oxygen-poor haemoglobin behave differently in a (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



Electroencephalograph (= EEG), magnetoencephalography (= MEG)

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



Fig: Wikimedia Commons, public domain



- Neurons interact electrically
- **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?

Recipe from Sally Butcher: Snackistan

Chorba frik ALGERIAN STREET SOUP

This is a bit like the Moroccan *harira*, but with meat. Simple-but-filling, spicy soups like this are especially popular during Ramadan and are common street fare during that month. The word *chorba* just means soup, and is used in differently spelled incarnations all the way from Kyrgyzstan to the Maghreb.

Freekah is green smoked wheat: it is available in good Middle Eastern stores (we can recommend one*), but you can easily substitute barley, which takes about the same time to cook.

SERVES 6

100g/3½ oz/½ cup dried chickpeas
(or use 1 can/400g/14oz)

1 large onion, diced

splash of oil, for frying

350g/12oz finely diced lean lamb

2 sticks of celery, finely chopped

1 carrot, grated

2–3 garlic cloves (although this is often avoided during Ramadan itself as it a) makes you thirsty, and b) is deemed disrespectful to smell of food during the month of fasting)

Soak the chickpeas overnight (or at least for 6 hours), then drain.

Fry the onion in some oil, then add the lamb and celery, stirring well. When the lamb is sealed all over and the celery has begun to soften, add the carrot, garlic and spices together with the drained chickpeas (if using dried); after a few minutes more, pour in the cold water, bring to the boil, then turn down the heat and simmer for about 1¼ hours, or until the meat and pulses are just cooked.

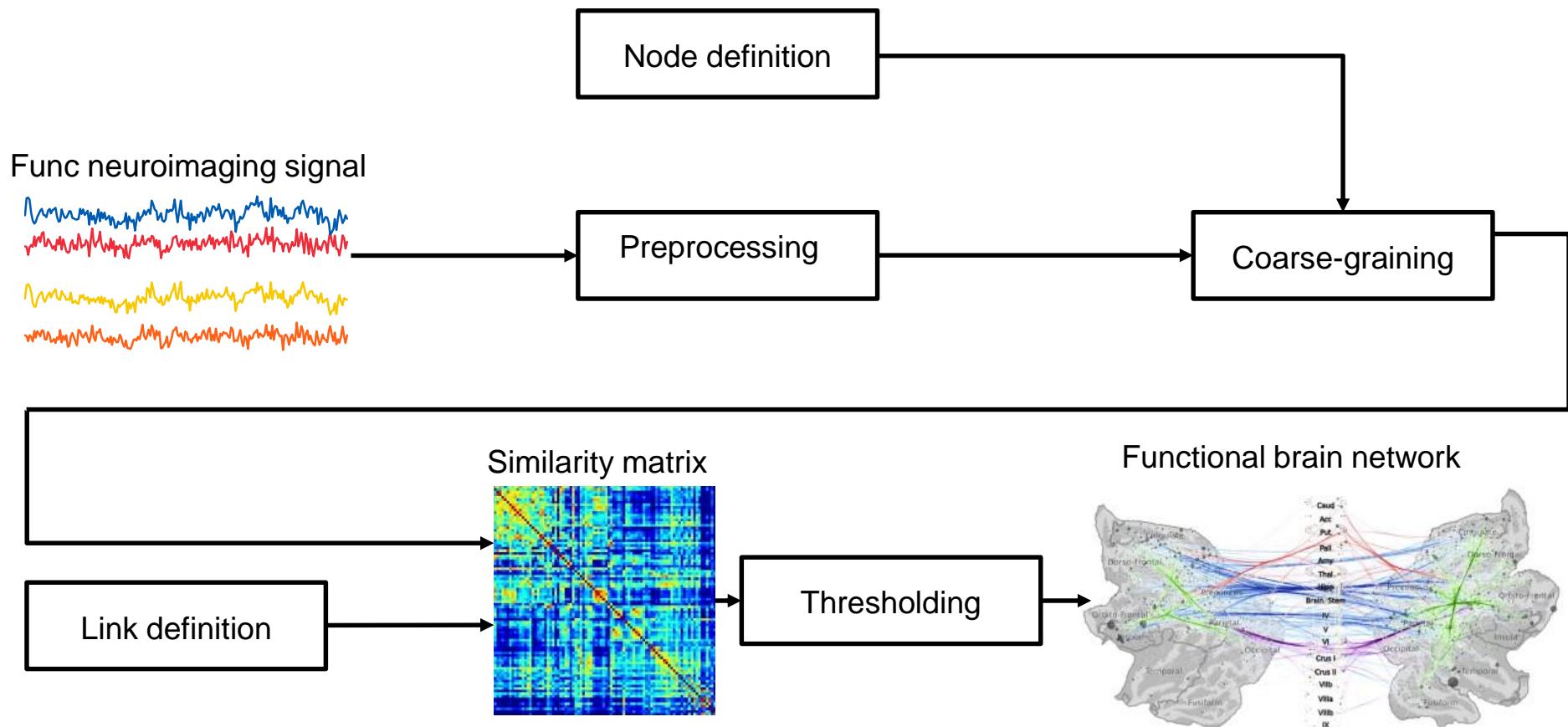
1 tsp ground cinnamon
½ tsp ground black pepper
½ tsp ground turmeric
1.5 litres/2½ pints/6½ cups water
1 tbsp tomato paste
125g/4½ oz freekeh
6 tomatoes, skinned and chopped
(or use 1 can/400g/14oz)
1 small bunch of fresh coriander (cilantro),
chopped
salt

A simple recipe:

Weighted networks from time series

1. Define nodes (each one with a time series)
2. Define link weights (measures of time series similarity)
3. Define threshold, discard sub-threshold links

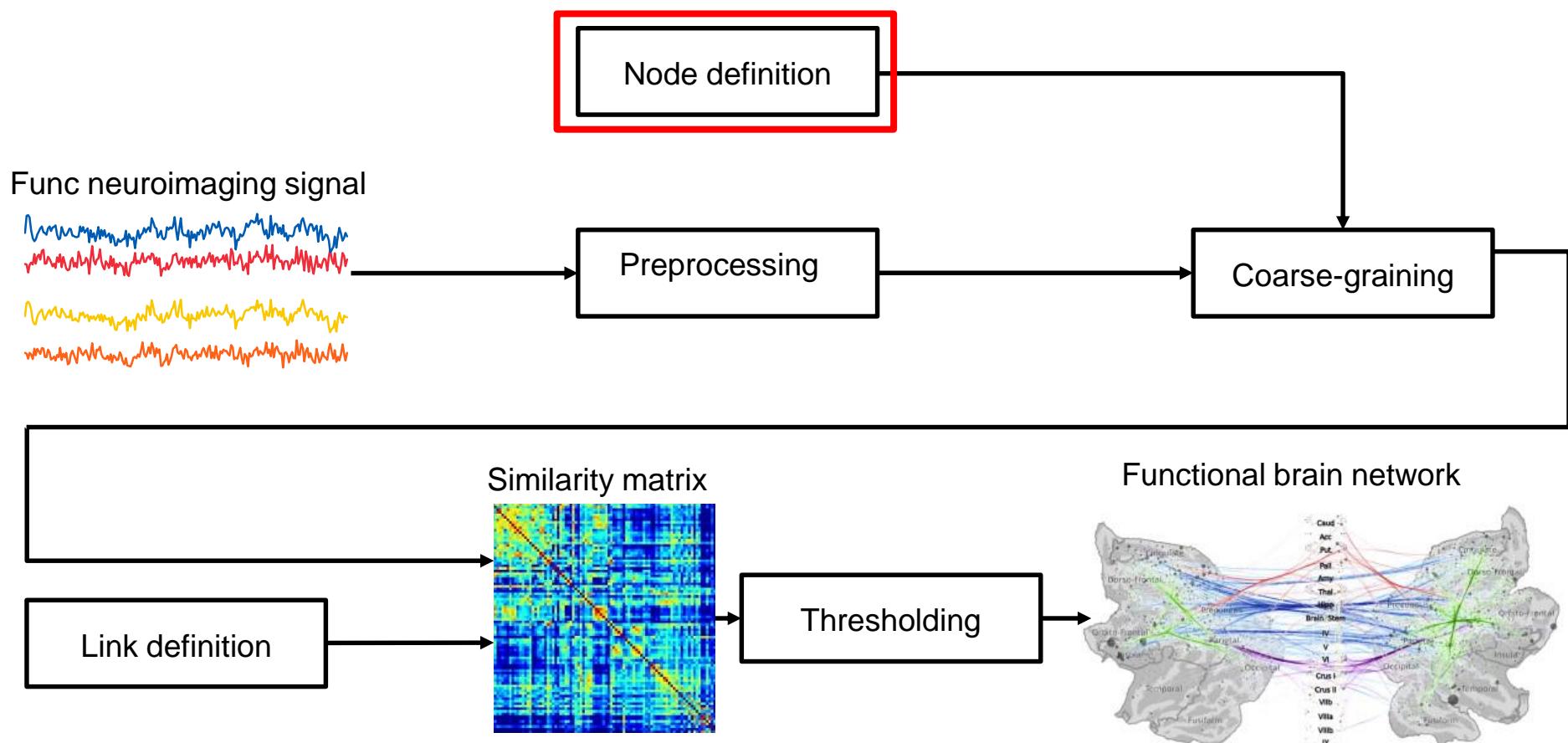
Functional networks: how-to?



Network from Nummenmaa et al. 2014, 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 scale of neurons

=> huge variation in node definition

- Number of nodes: from < 100 to 10^5

Node definition affects network properties (e.g. Wang et al. 2009)

Common strategies (for a review, Korhonen et al. 2021, section 3.2):

- 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:

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

More on this:

- Korhonen et al. 2017
- Ryyppö et al. 2018

Violent?

How correlated are voxels of a ROI?

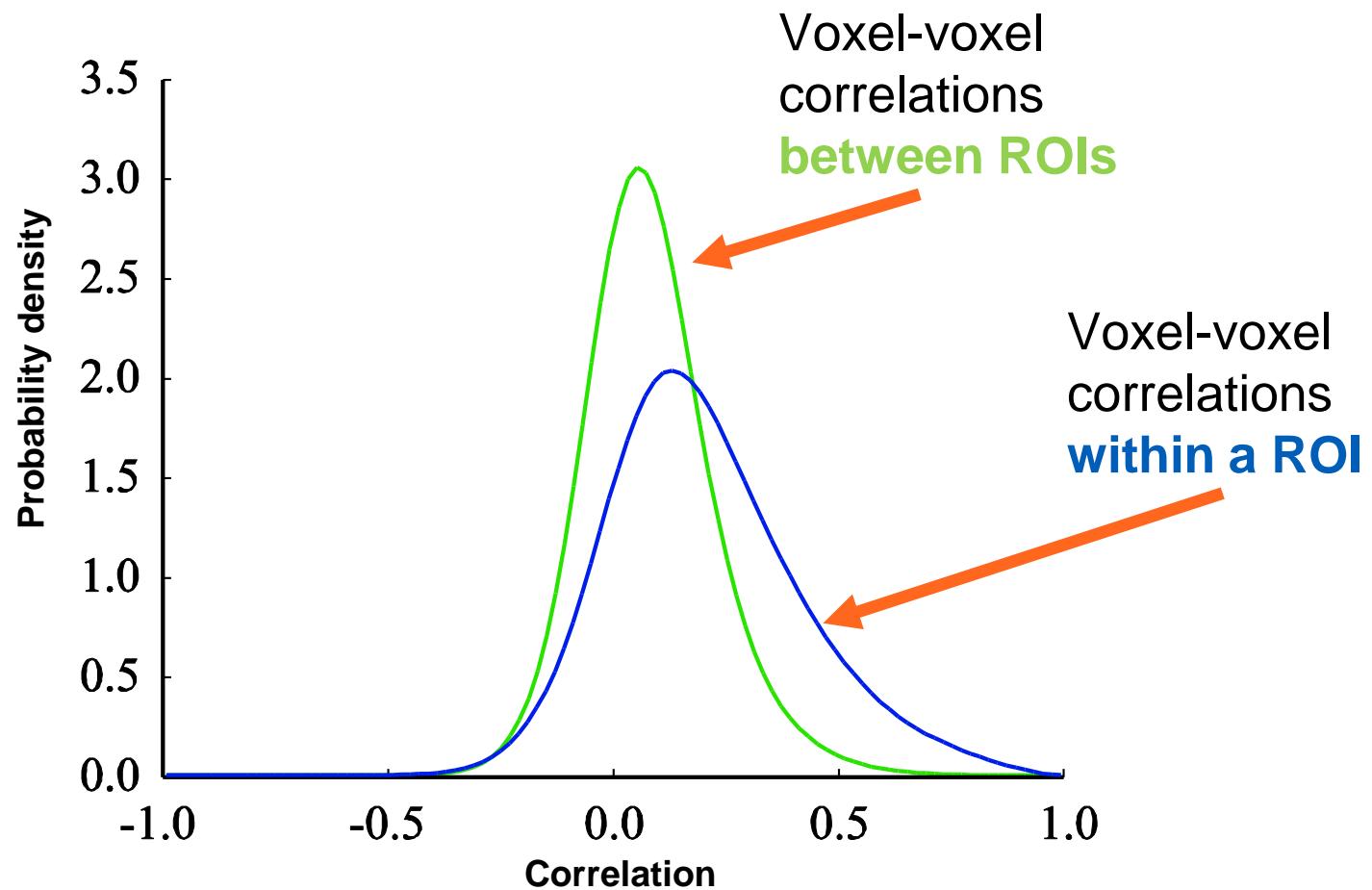
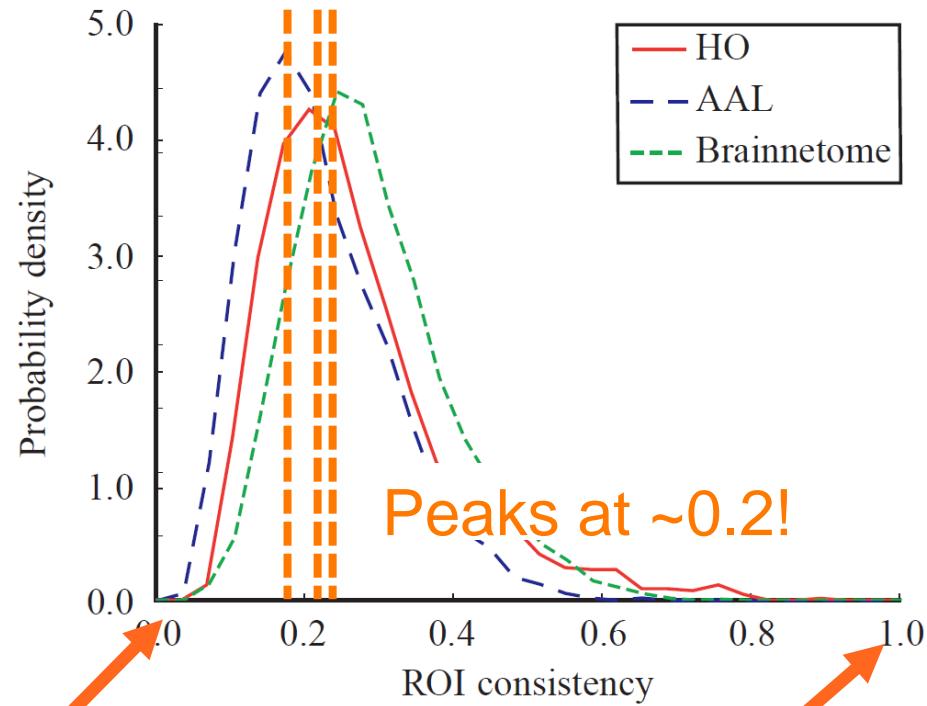


Fig: Korhonen et al. 2017

How homogeneous are ROIs?

Fig: Korhonen et al. 2017



Spatial consistency

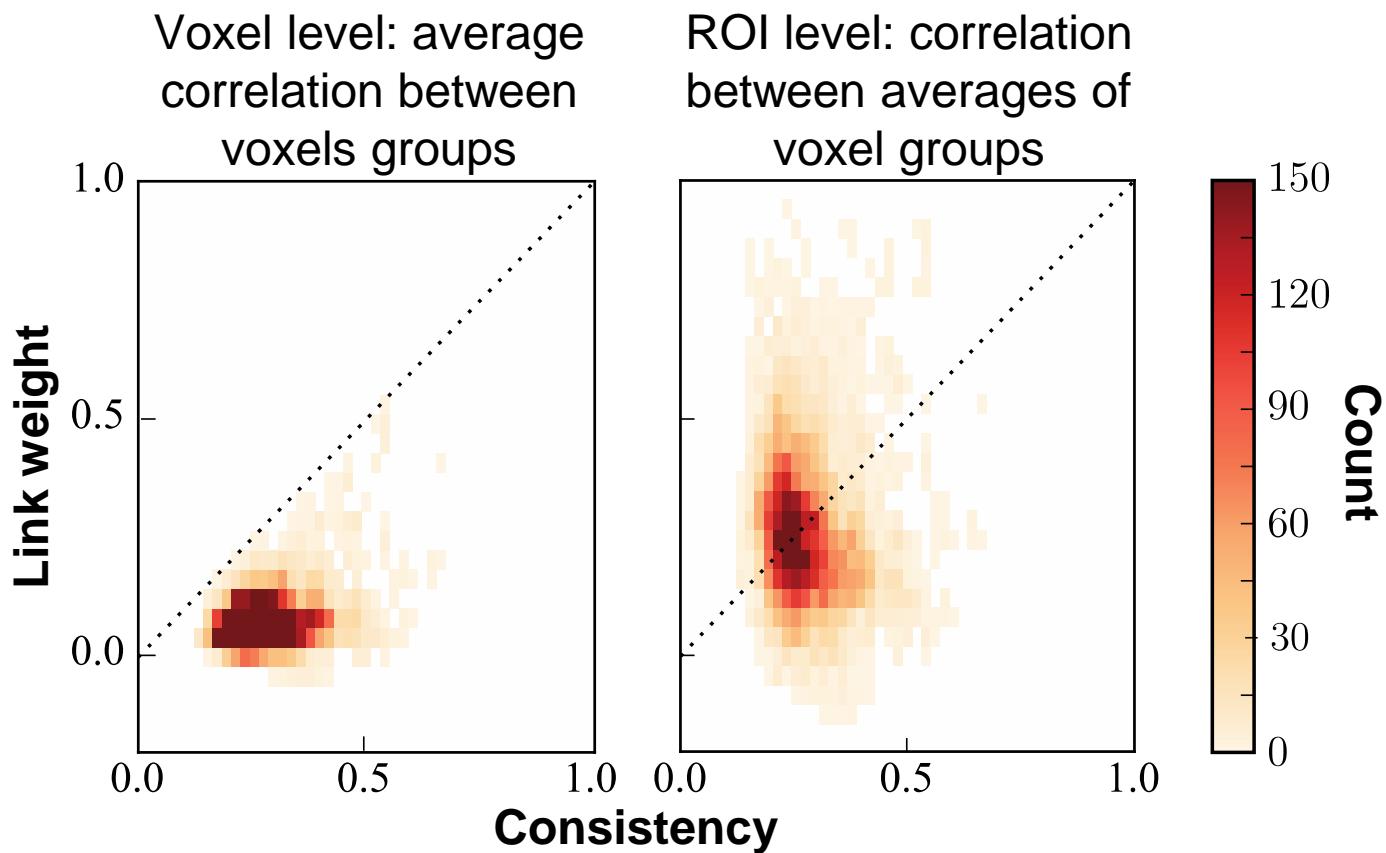
= measure of functional
homogeneity:

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

Lack of
homogeneity

Perfect
homogeneity

Does consistency predict connectivity?



Does consistency predict connectivity?

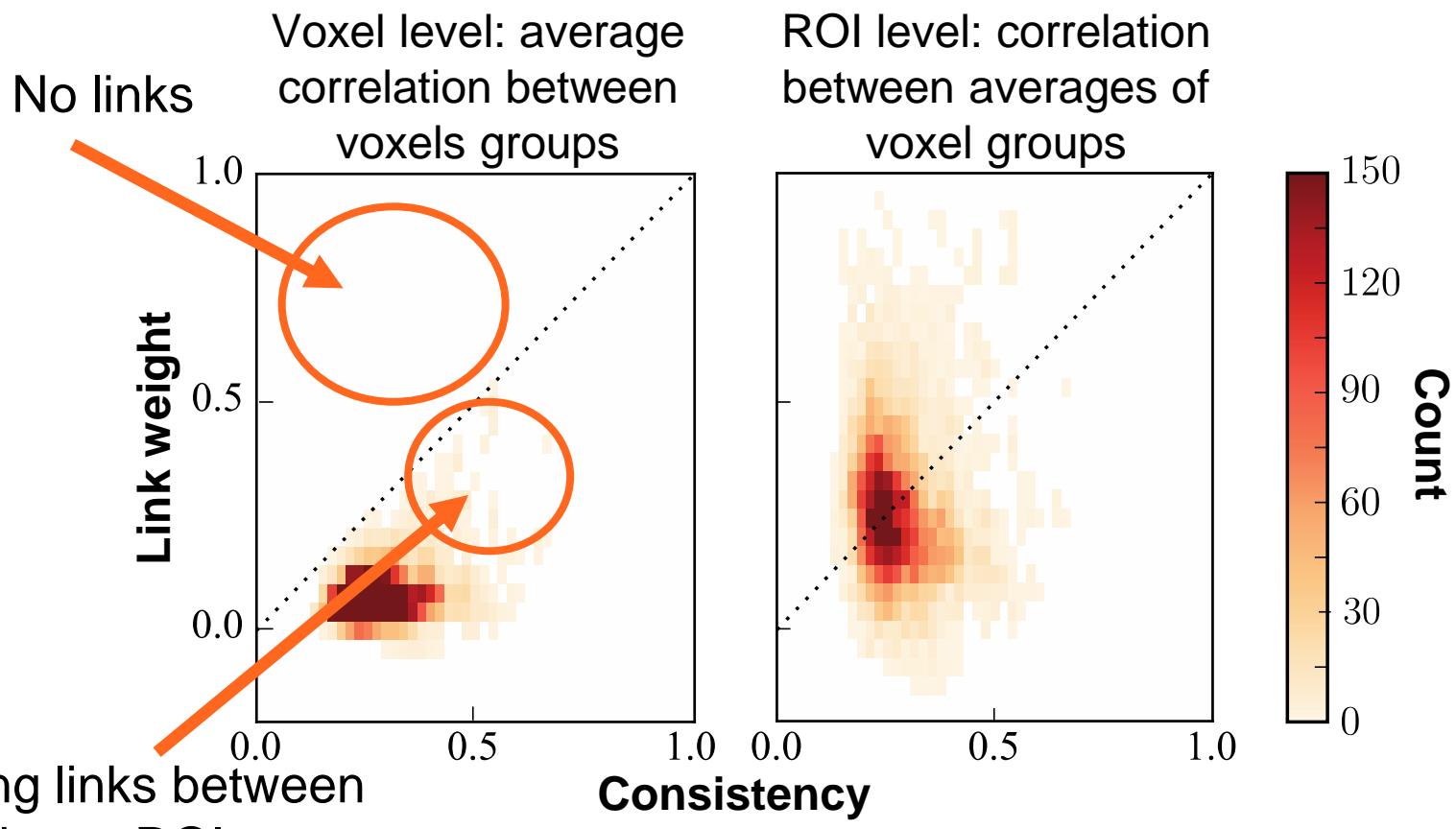
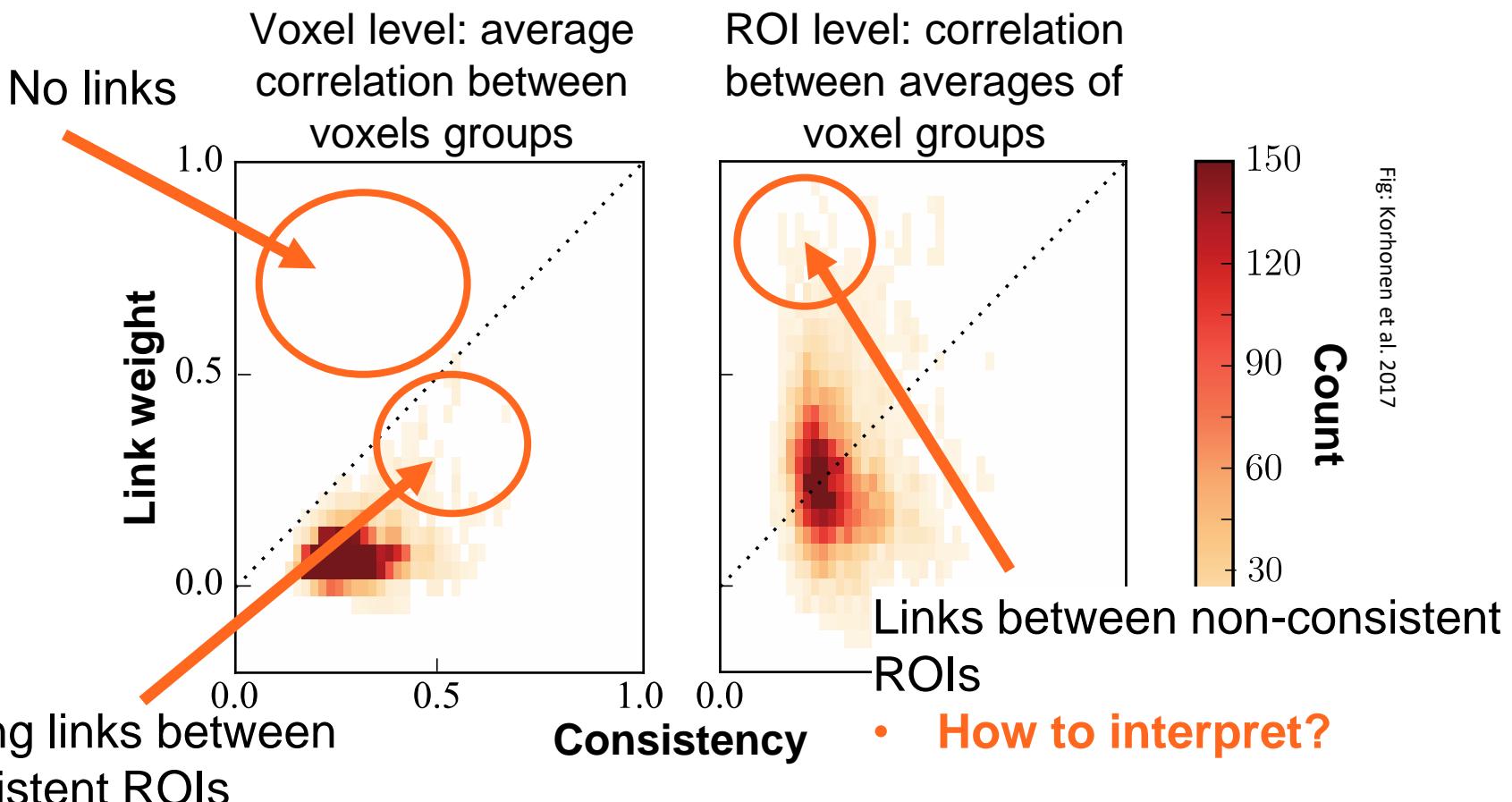


Fig: Korhonen et al. 2017

Does consistency predict connectivity?



ROIs have rich internal connectivity structure

High spatial consistency

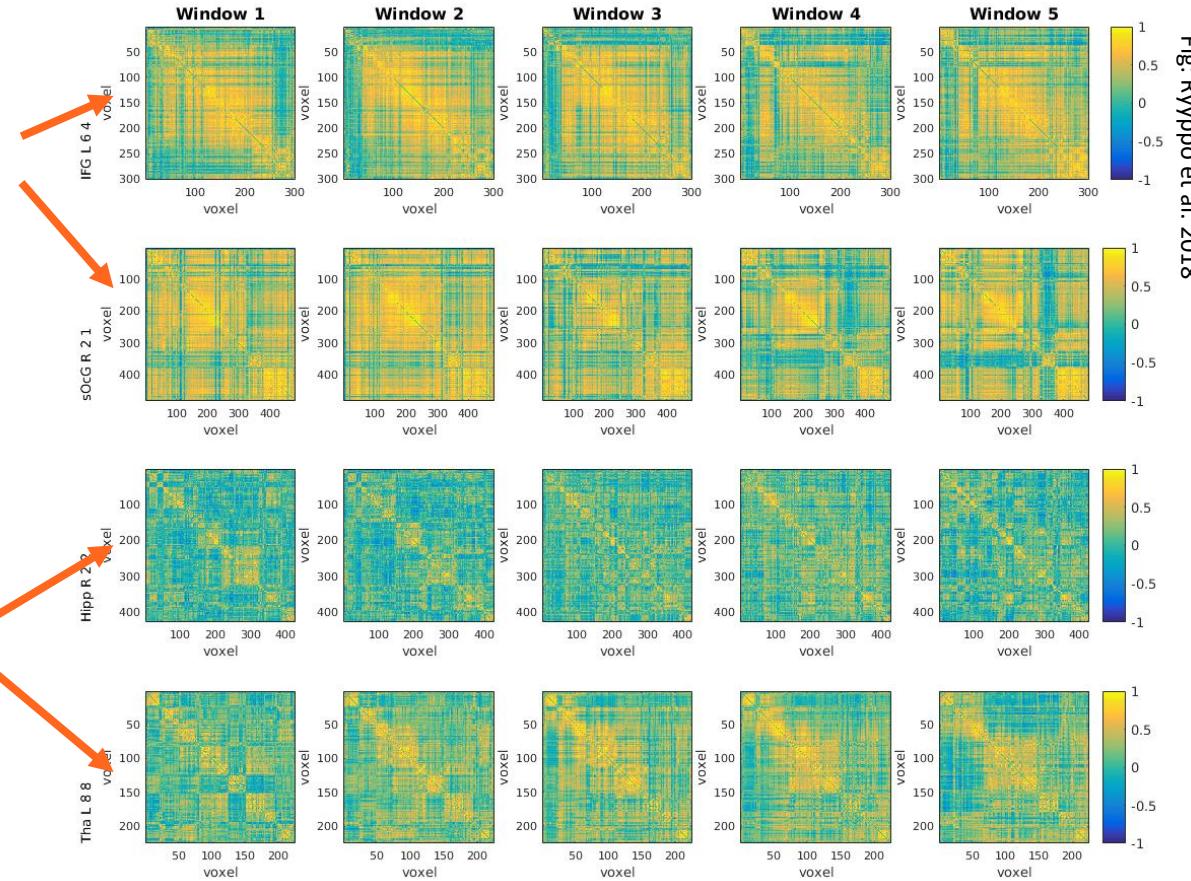
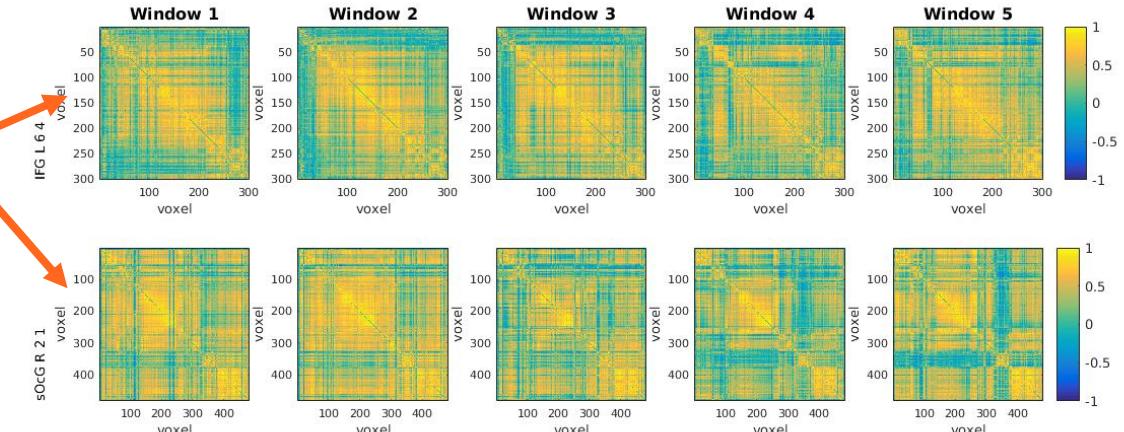


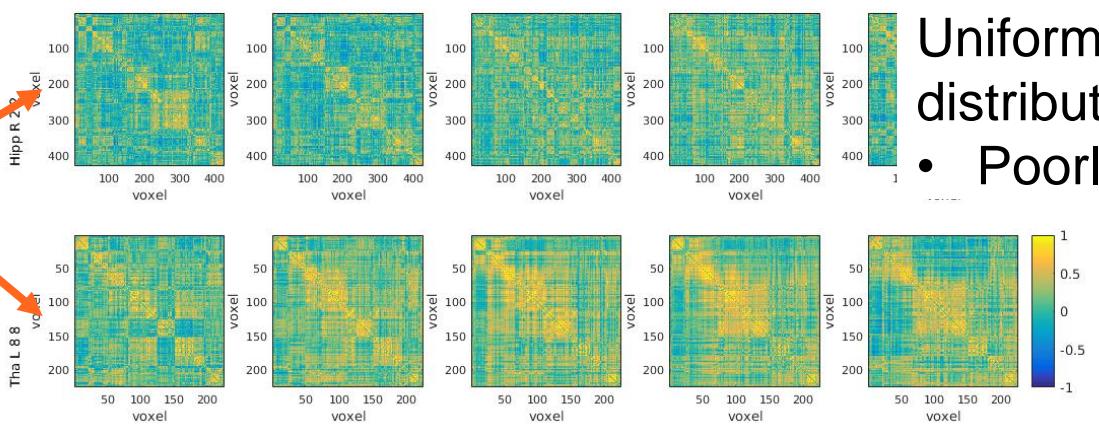
Fig: Ryvuppo et al. 2018

ROIs have rich internal connectivity structure

High spatial consistency



Low spatial consistency

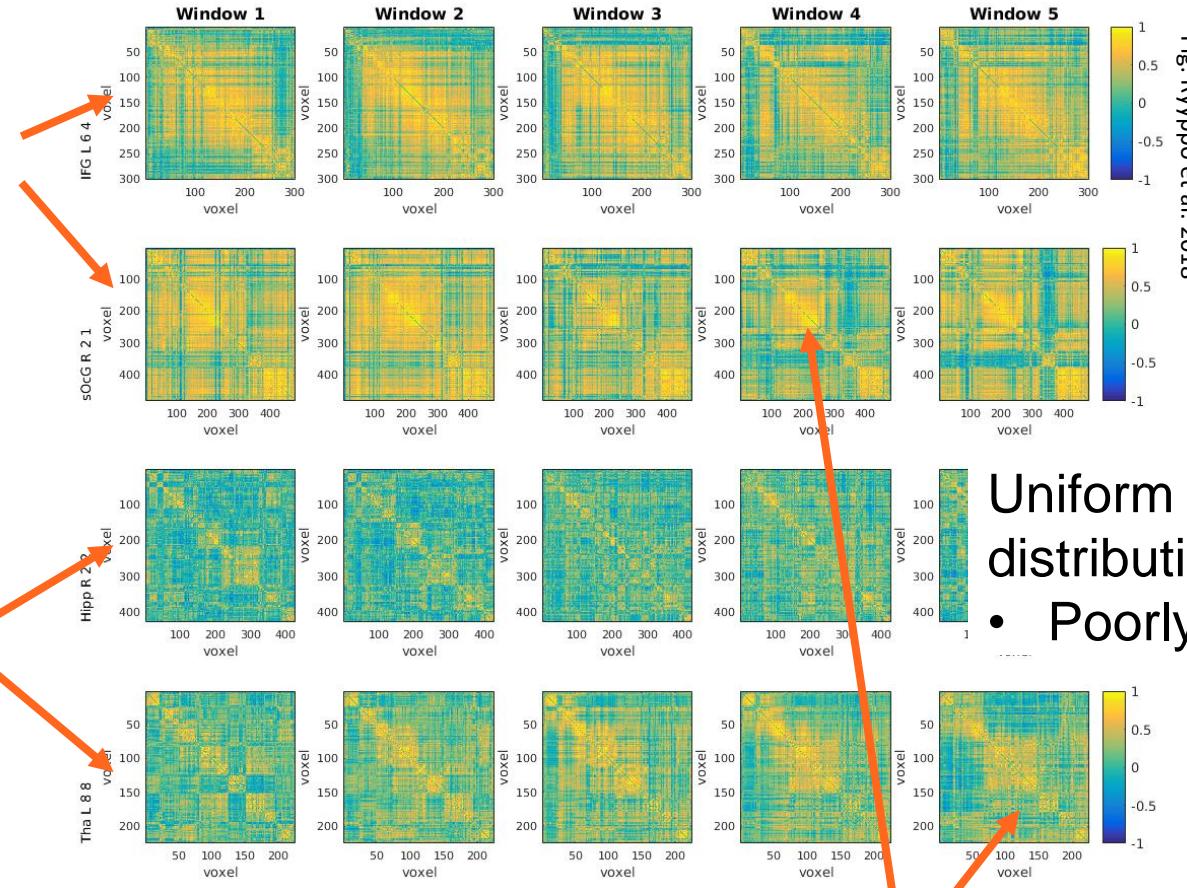


Uniform correlation distribution

- Poorly defined ROI?

ROIs have rich internal connectivity structure

High spatial consistency



Low spatial consistency

- Fig: Ryvpon et al. 2018
- Uniform correlation distribution
 - Poorly defined ROI?
 - Intra-ROI modules
 - Network topology?

ROIs have rich internal connectivity structure

High spatial consistency

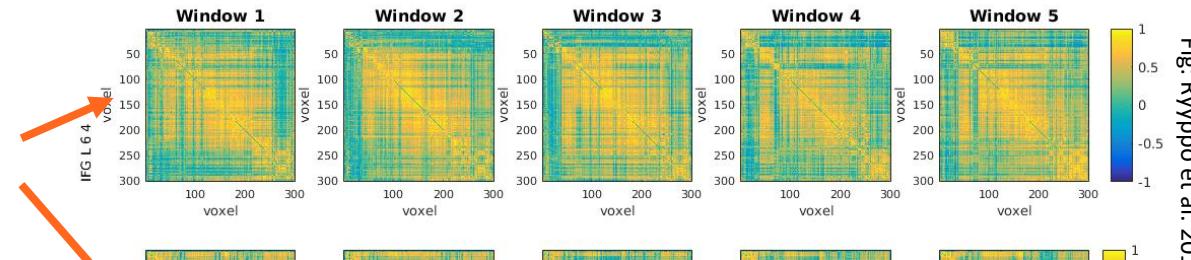
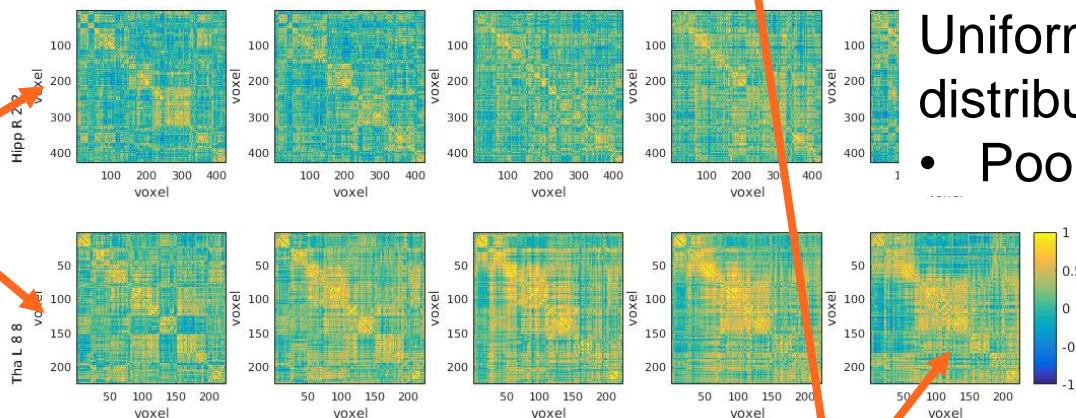


Fig. Kyyppö et al. 20..

Ignored by current network construction pipelines!

Low spatial consistency



- Uniform correlation distribution**

 - Poorly defined ROI?

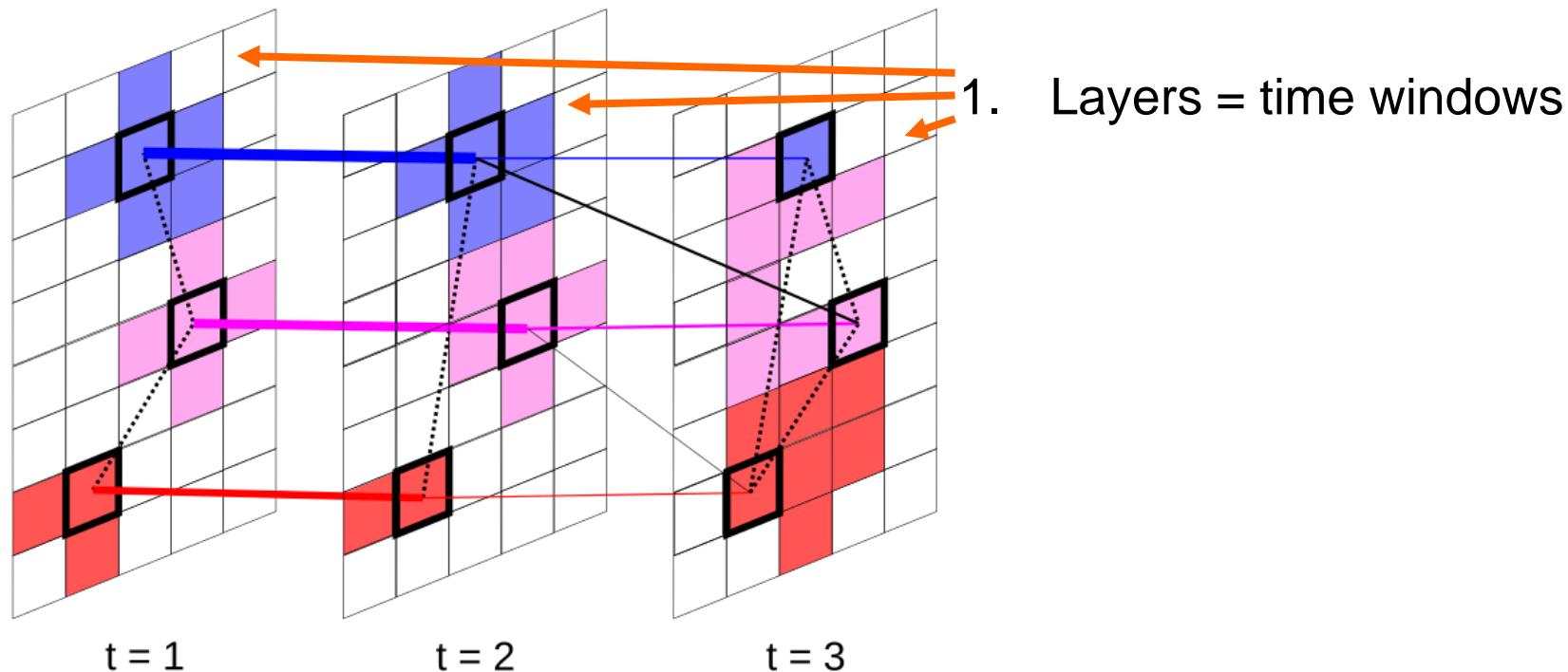
Intra-ROI modules

 - Network topology?

Possible solution: time-dependent nodes

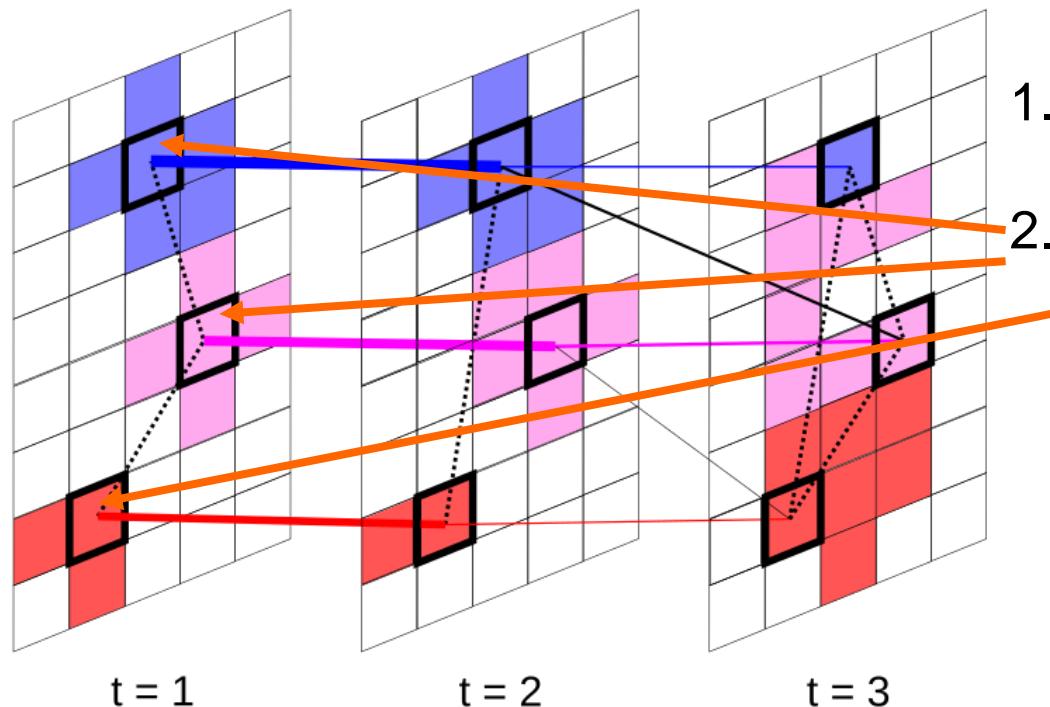
(On-going, with T. Nurmi, M. Hakonen, I. Jääskeläinen & M. Kivelä)

Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



Possible solution: time-dependent nodes

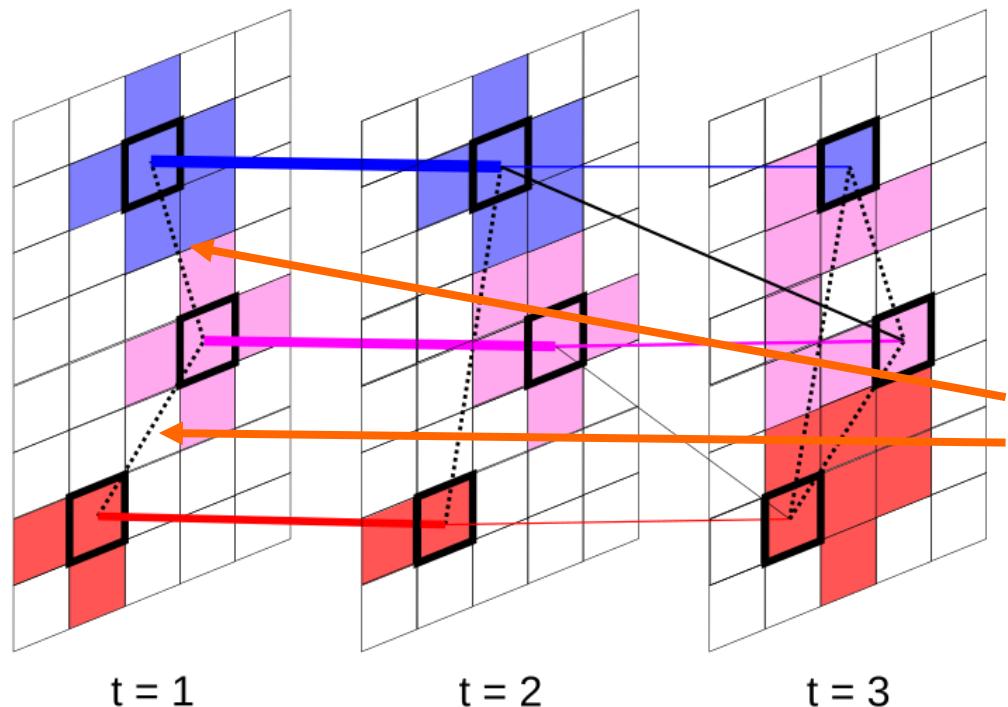
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)

Possible solution: time-dependent nodes

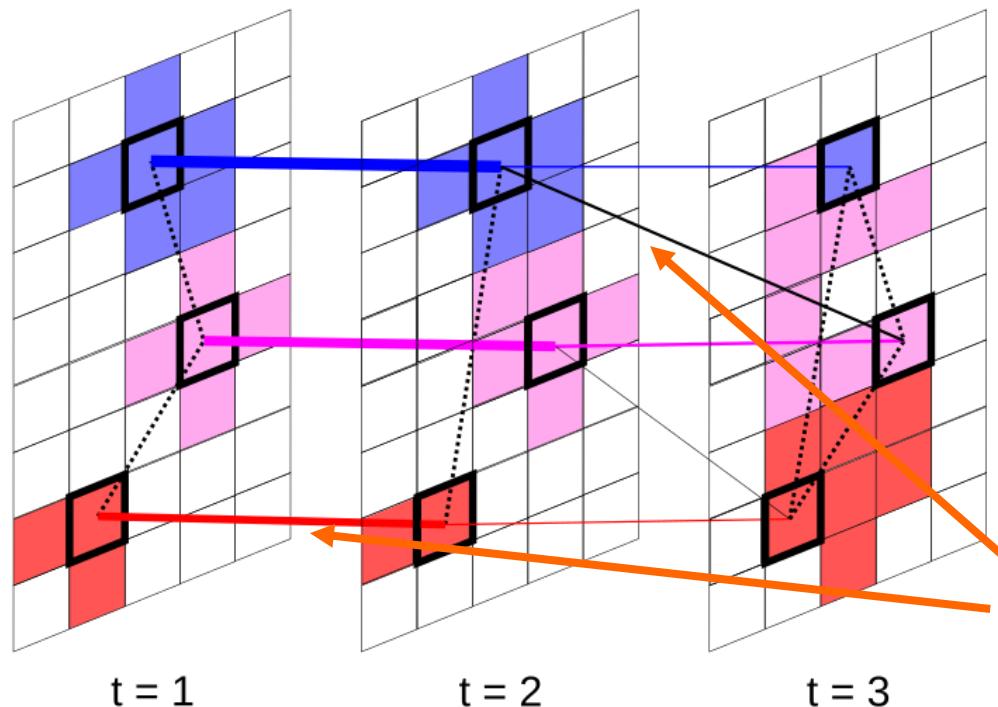
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



1. Layers = time windows
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3. Intralayer links = Pearson correlation

Possible solution: time-dependent nodes

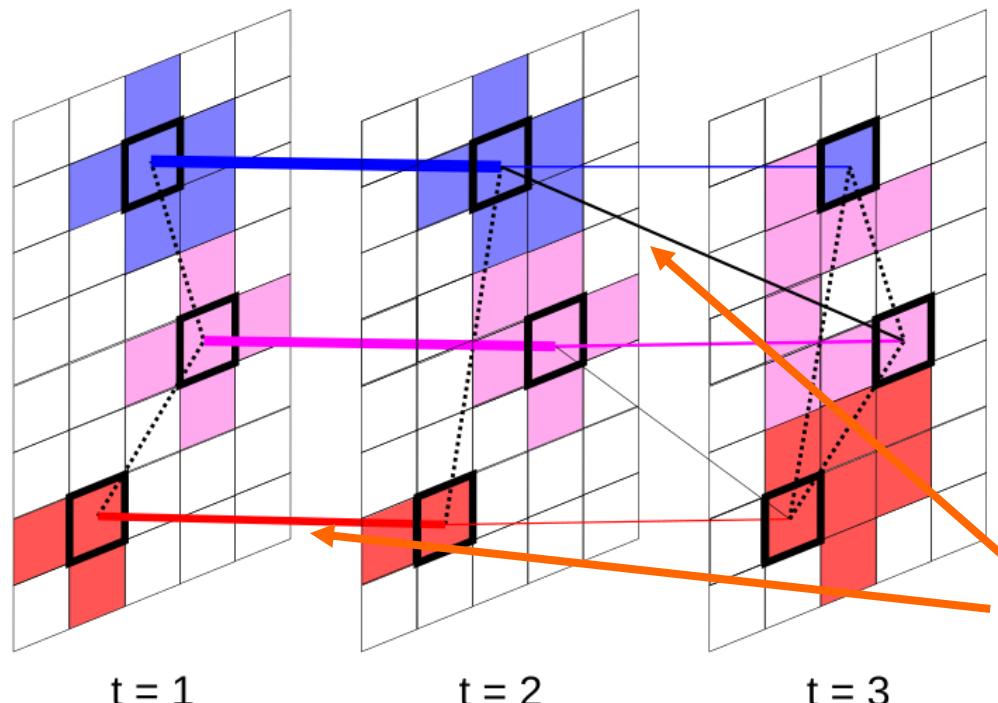
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)
3. Intralayer links = Pearson correlation
4. Interlayer links = spatial overlap

Possible solution: time-dependent nodes

Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)
3. Intralayer links = Pearson correlation
4. Interlayer links = spatial overlap

Questions:

- How do ROIs change over time? Splitting, merging, disappearing?
- State changes?
- What about Alzheimer's disease?

Conclusions

- Network theory helps to understand the (human) brain
- Network construction is not trivial
 - Node definition?
 - Not covered today: preprocessing, link definition, thresholding?
 - **Know your methods!**
- Brain networks change in time
 - Traditonally, network dynamics are ignored
 - Including time opens new horizons
 - Example: time-dependent nodes
- Not all that glitters is a network – is the (human) brain?
 - **Needed: critical thinking & discussion**

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Thank you!

Questions, comments?

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Slides: github.com/onerva-korhonen/presentations/blob/master/uppsala-310522.pdf