Aalto University
School of Science

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

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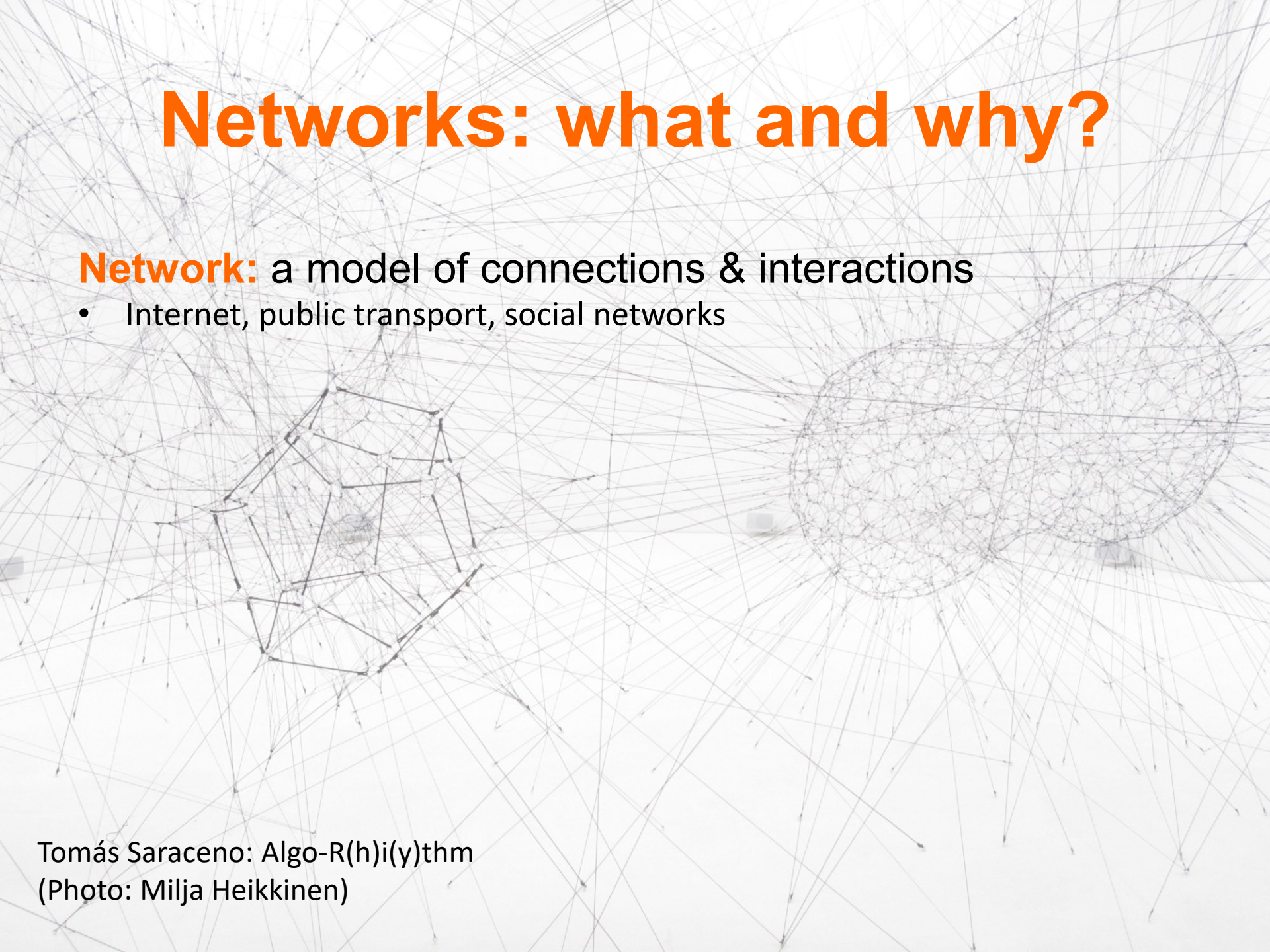
onervakorhonen.wordpress.com, @OnervaKorhonen
17.7.2023

Slides:
github.com/onerva-korhonen/presentations/blob/master/CNA_krakow_170723.pdf

Networks: what and why?

Network: a model of connections & interactions

- Internet, public transport, social networks



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

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- Web pages, stops, people

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

Tomás Saraceno: Algo-R(h)i(y)thm
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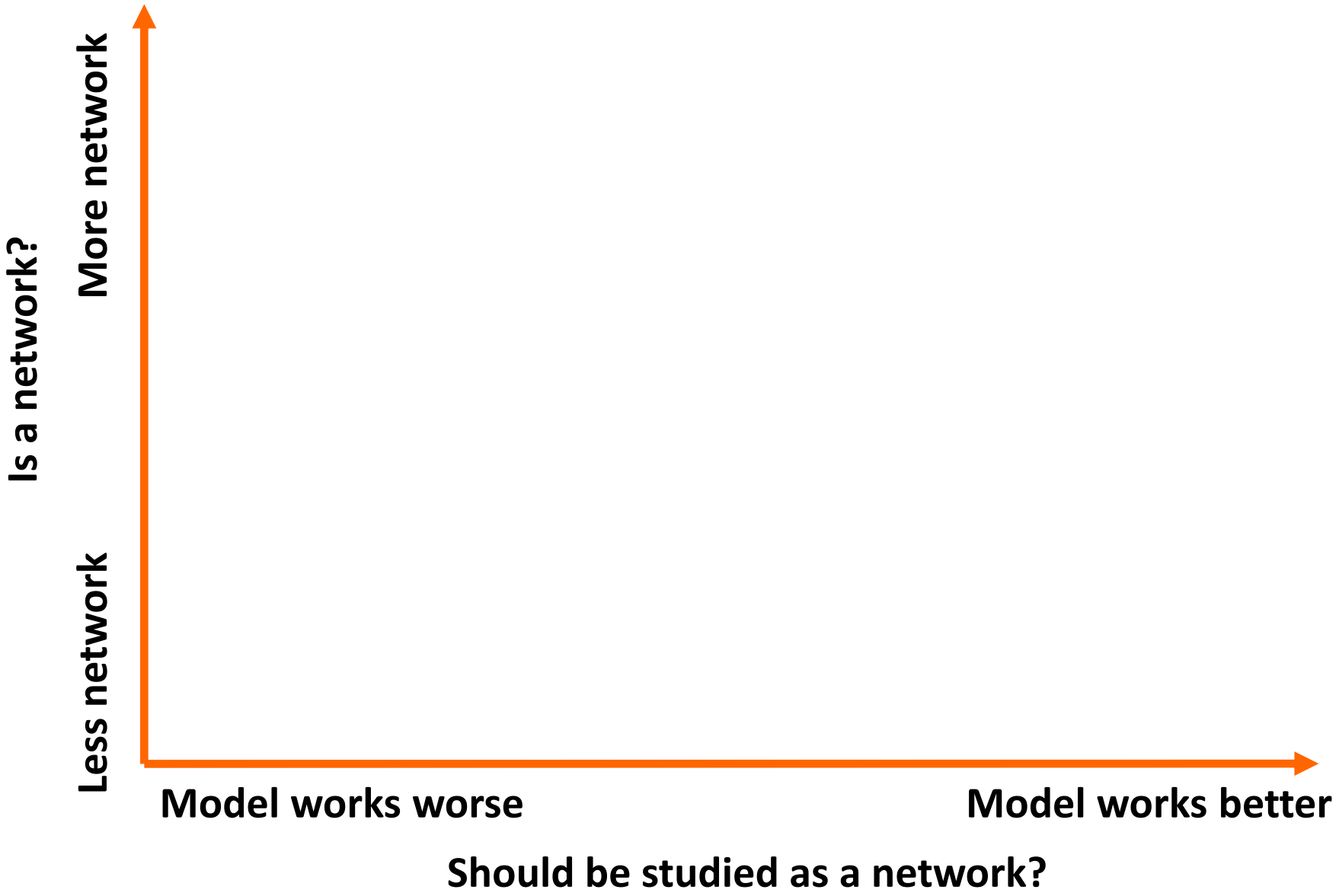
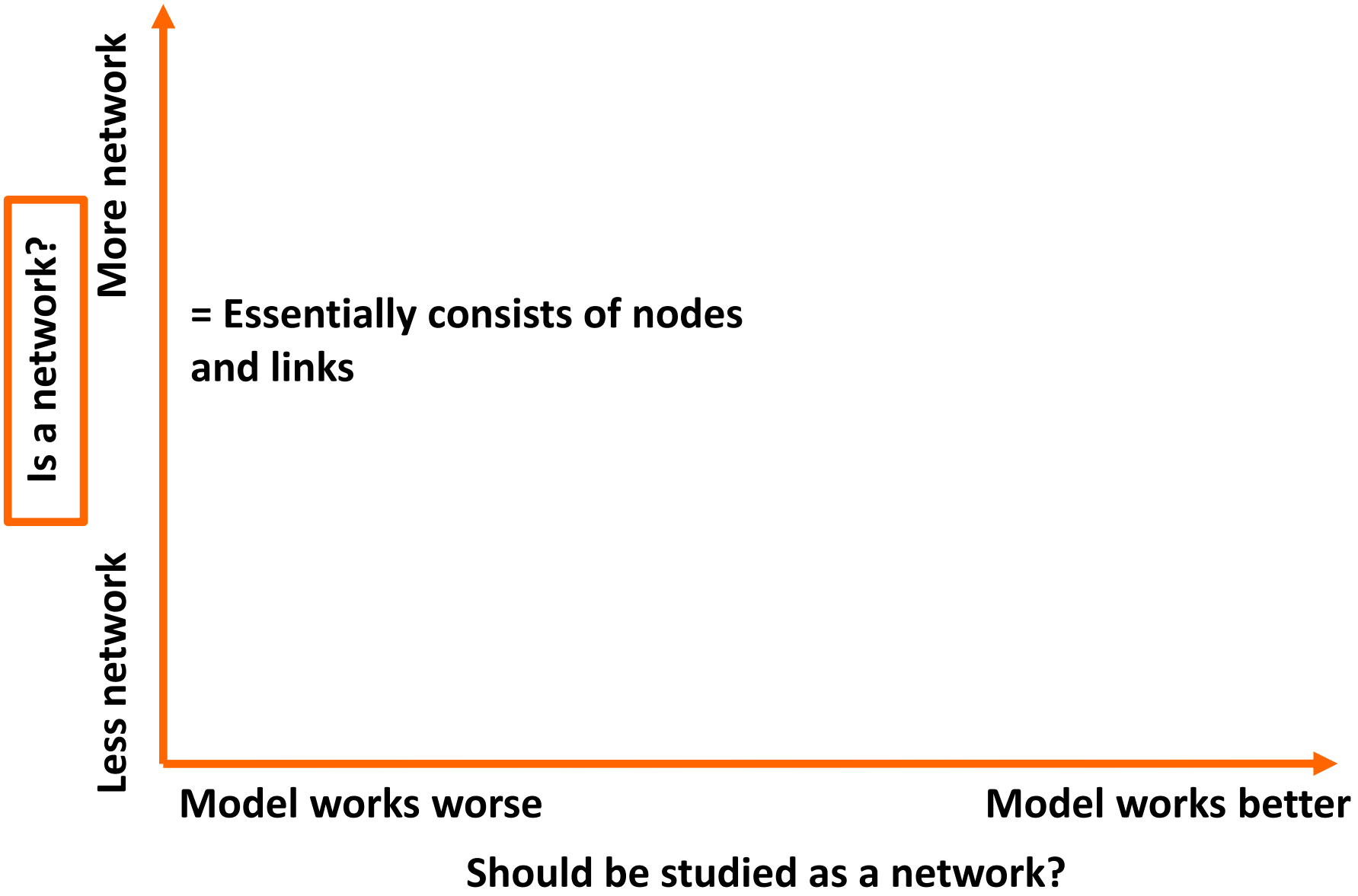
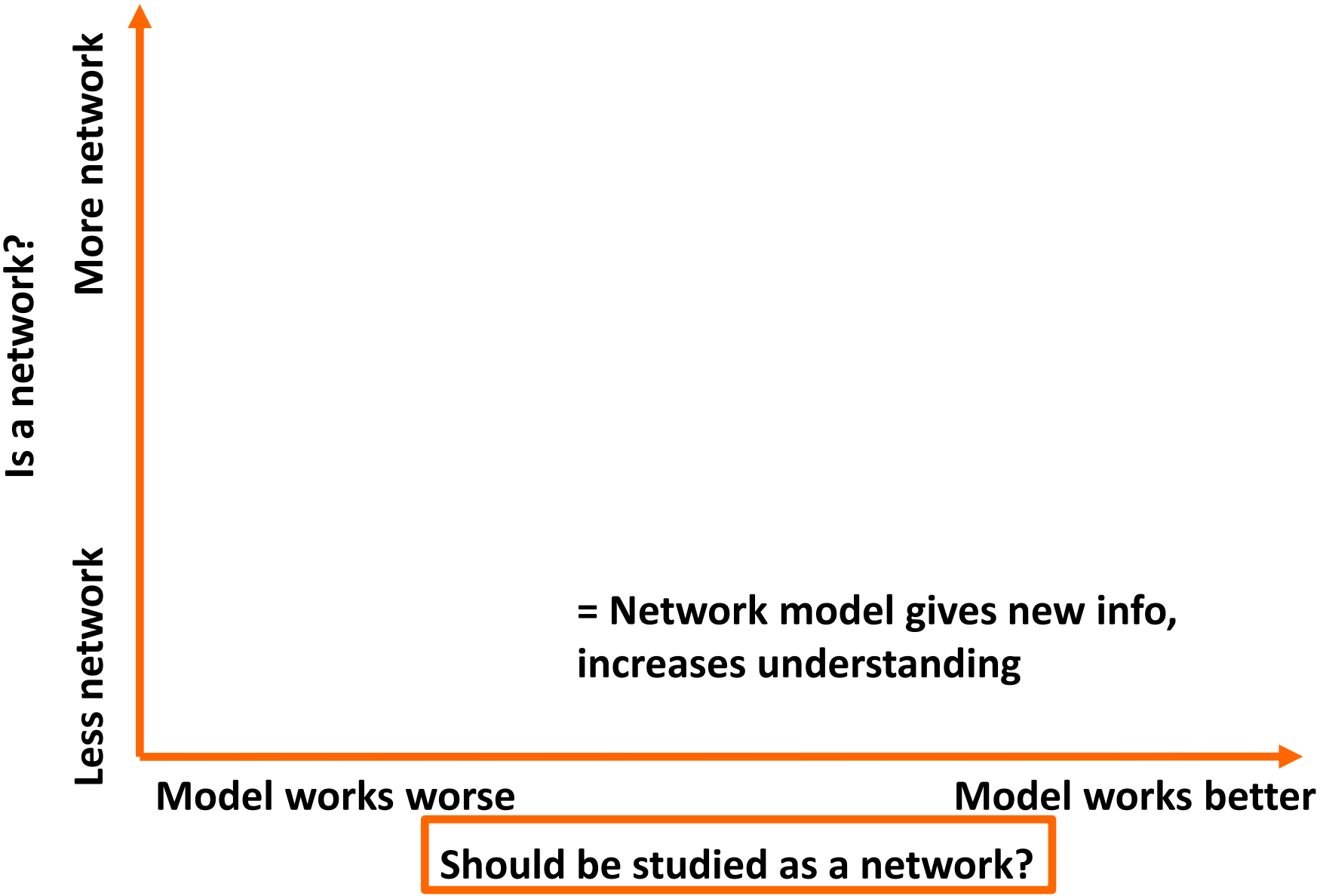
Not all that glitters is a network



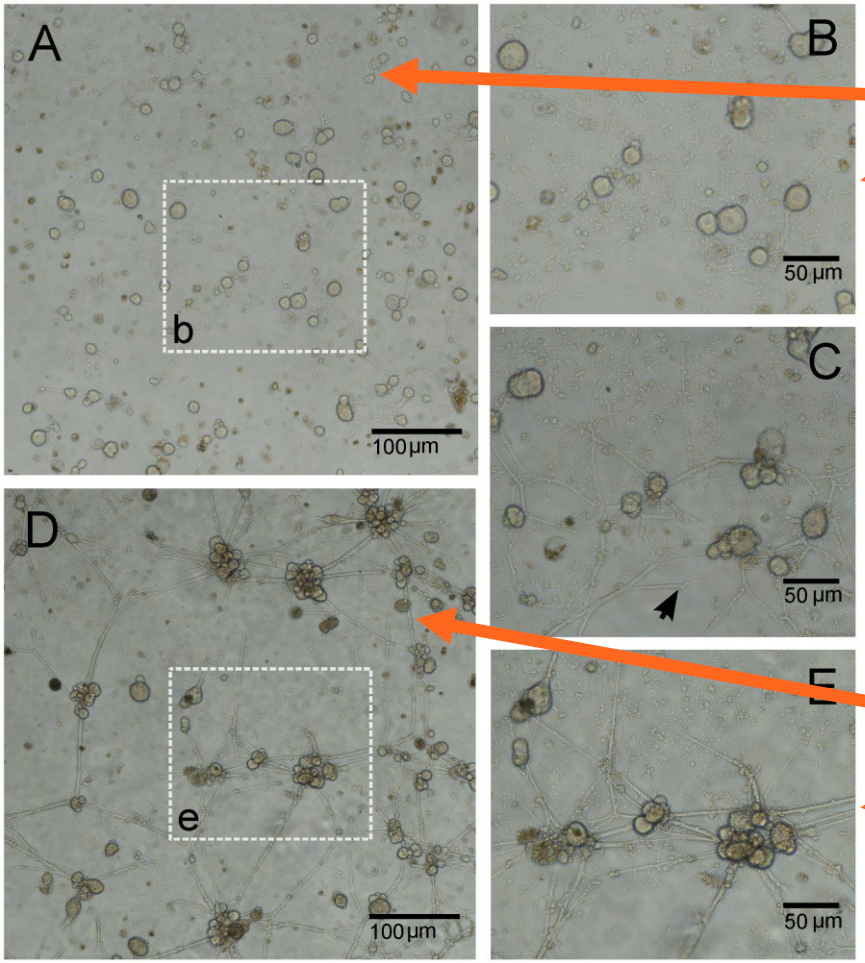

Is a network?
More network
Less network
= Essentially consists of nodes and links
Model works worse
Model works better
Should be studied as a network?


Is a network?
More network
Less network
= Network model gives new info,
increases understanding
Model works worse
Model works better
Should be studied as a network?

Brain networks: Why?

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

Fig: de Santos-Sierra et al. 2014, published under CC BY 4.0

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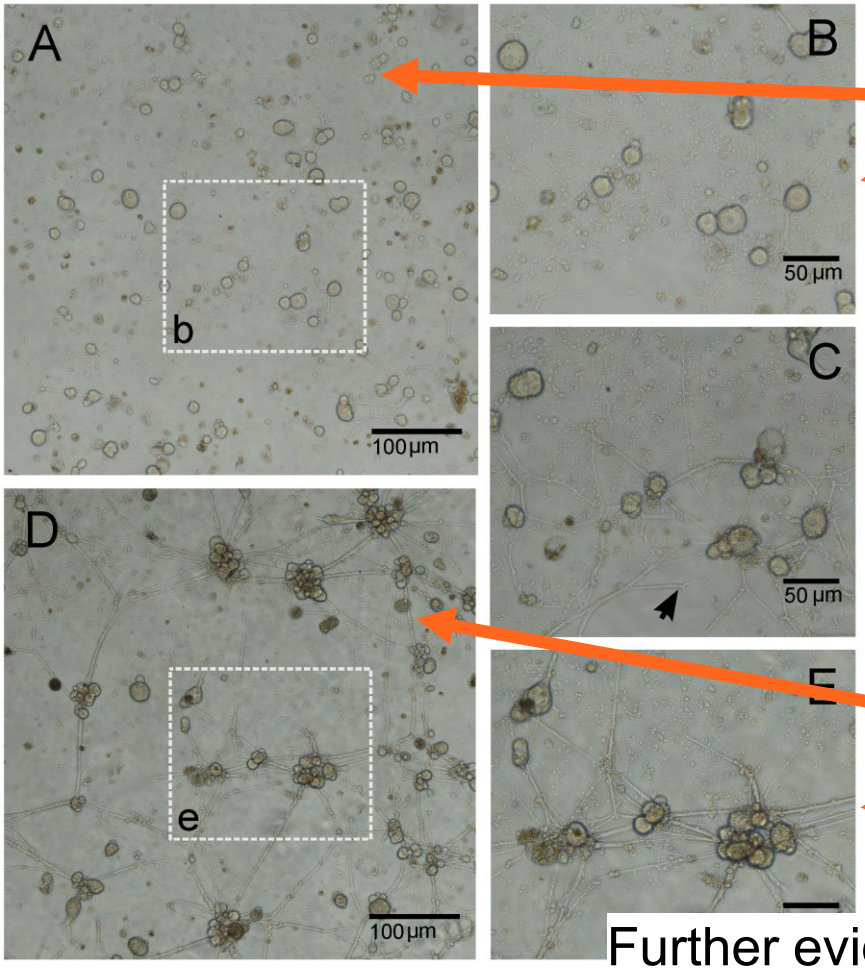


Day 3 after separating neurons: axon bundles start to grow

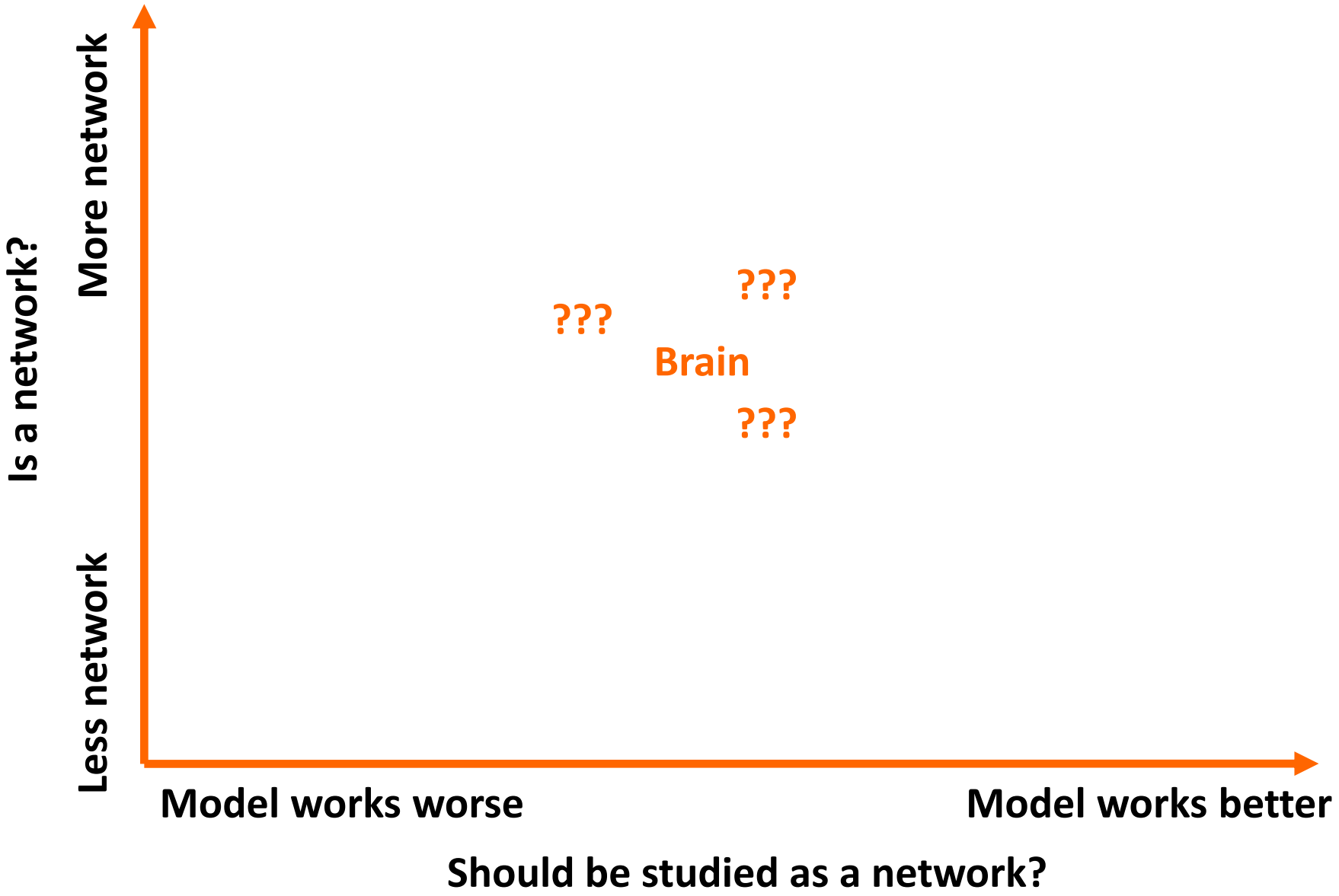
Day 6: non-connected neurons start to die

Day 12: a complex network of connected neurons

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

Fig: de Santos-Sierra et al. 2014. Emergence of sm
anatomical networks in self-organizing clustered ne
PLOS One 9(1): e85828, published under CC BY 4.0

Brain networks: What?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Brain
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Figs: Wikimedia Commons, public domain

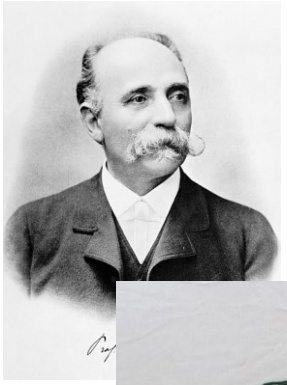

Photo: Milja Heikkinen

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Brain

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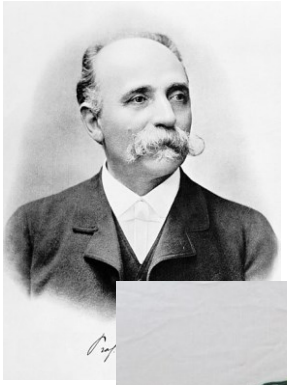

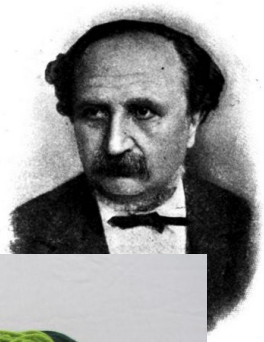

Photo: Milja Heikkinen

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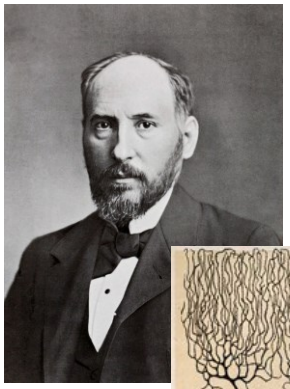

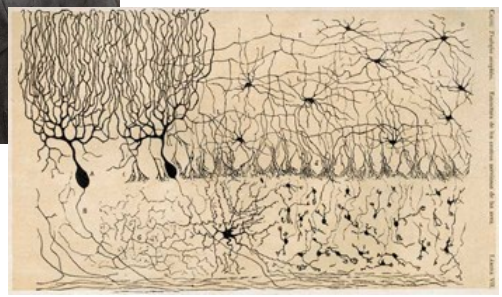

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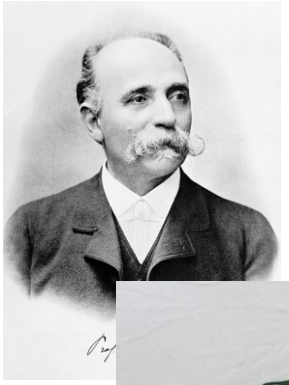

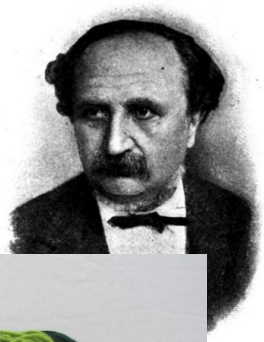

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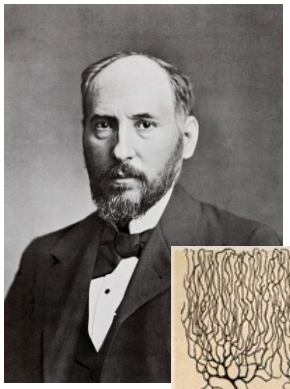

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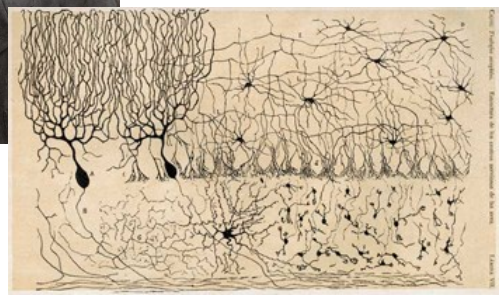

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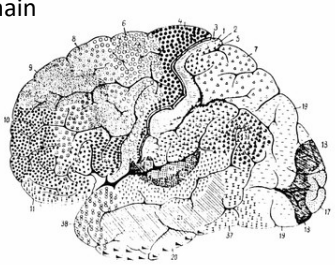

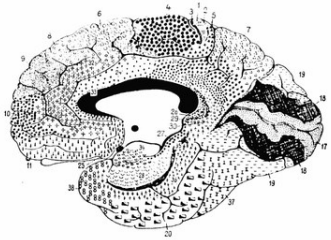

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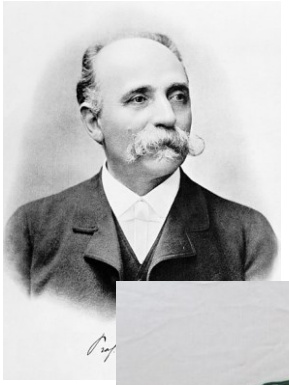

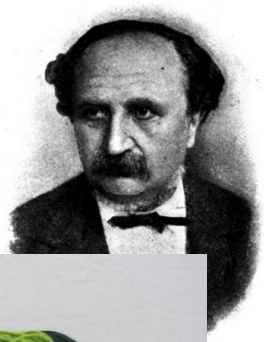

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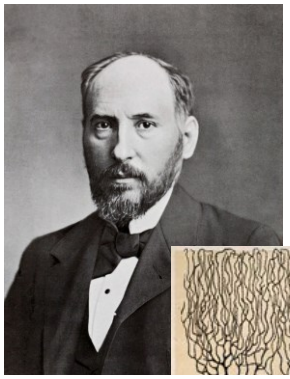

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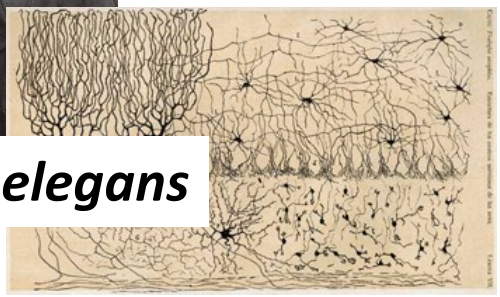

White et al. 1986: *C. elegans*

Brain

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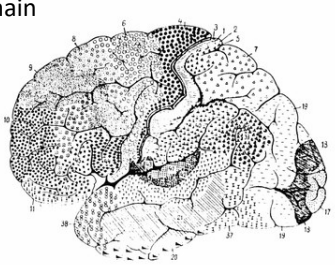

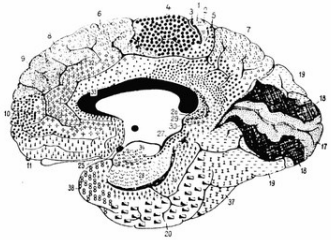

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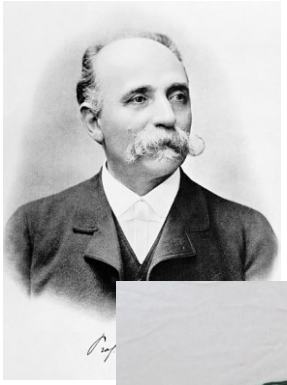

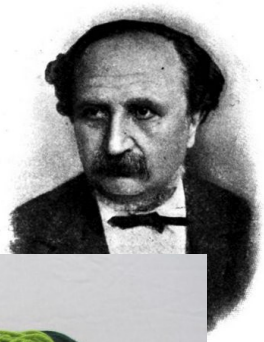

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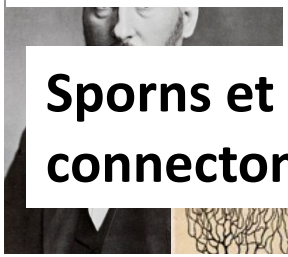
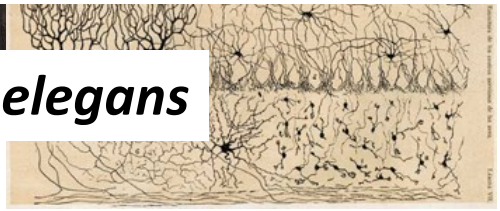


Bassett & Muldoon 2016, Bassett & Sporns 2017: network neuroscience

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



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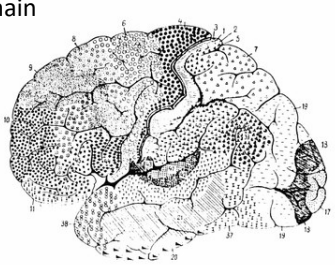
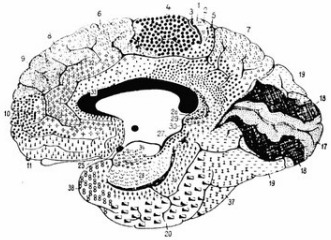




Is a network?

More network

Less network

Model works wors

Model works better

Should be studied as a network?

Network neuroscience

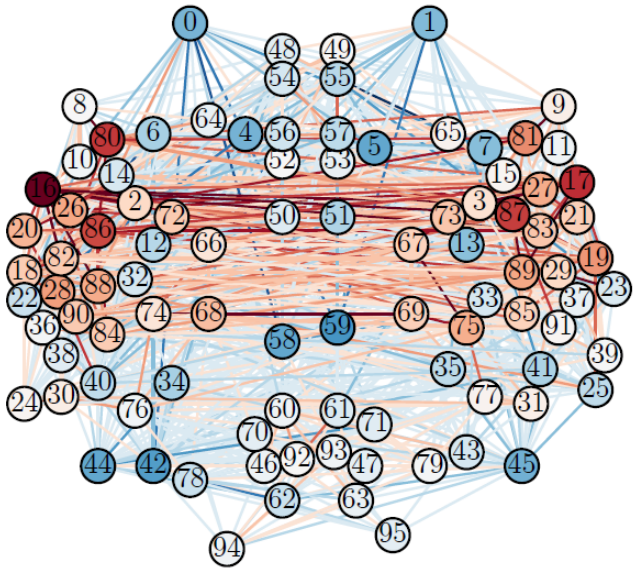
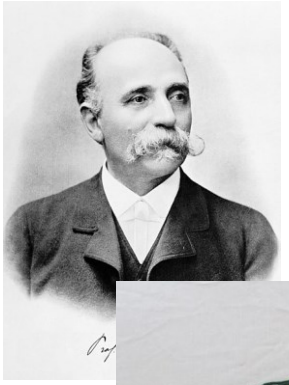
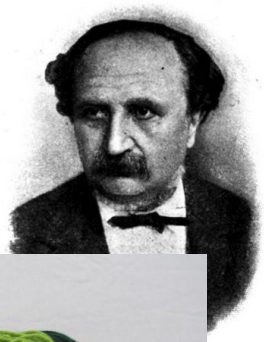


Fig: Alakörkkö *et al.* 2017, *European Journal of Neuroscience*

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

Figs: Wikimedia Commons, public domain





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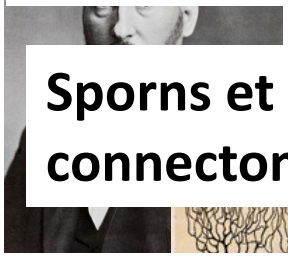

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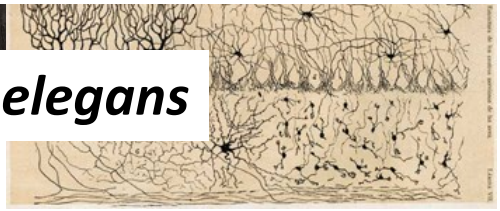

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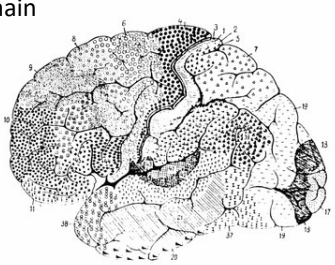
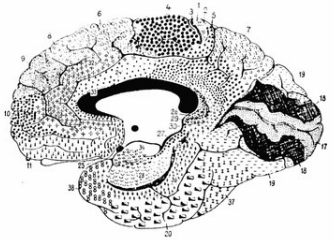




Is a network?

More network

Less network

how to define nodes/links?

structure/function?

correlation = causation?

Model works wors

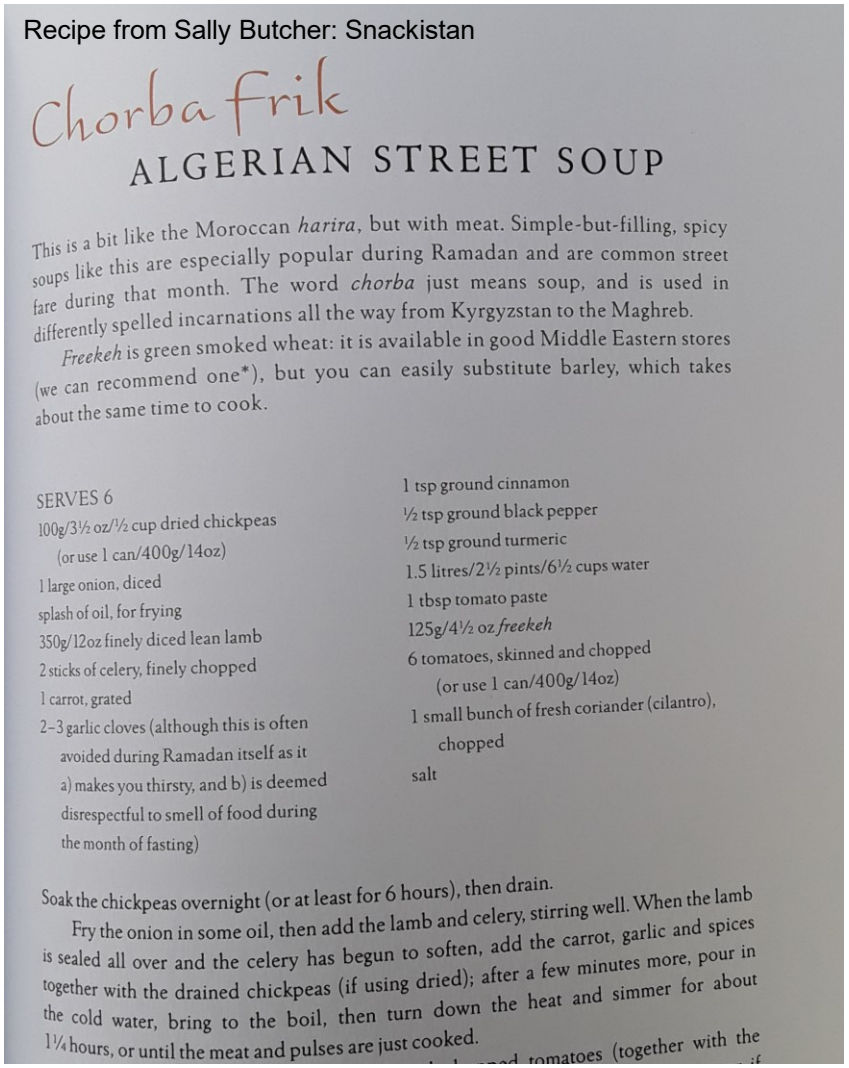
Model works better

Should be studied as a network?

Brain networks: How?

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.

Freekeh 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)
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

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.

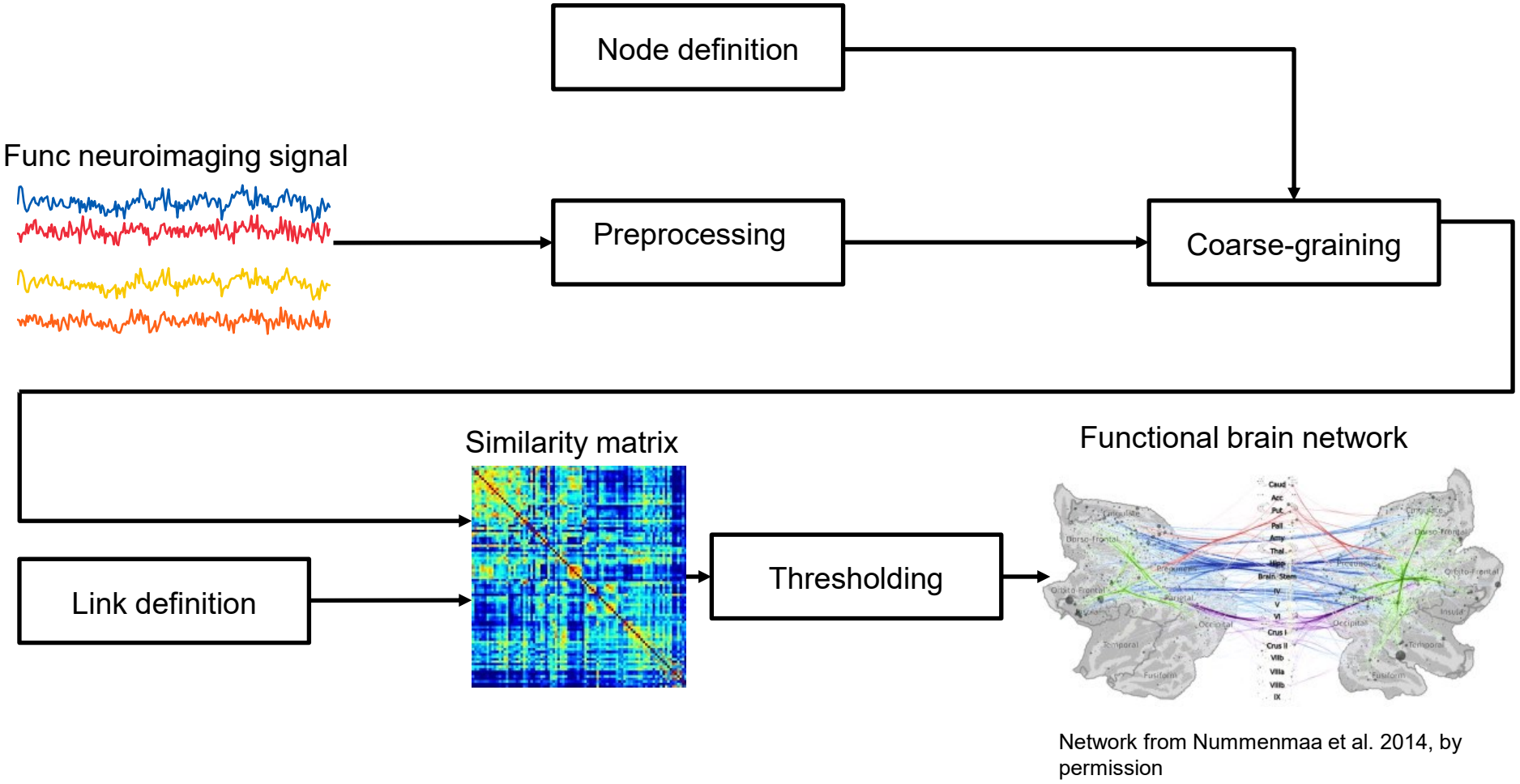
tomatoes (together with the

A simple recipe:

Weighted networks from time series (e.g. MEG, EEG, fMRI)

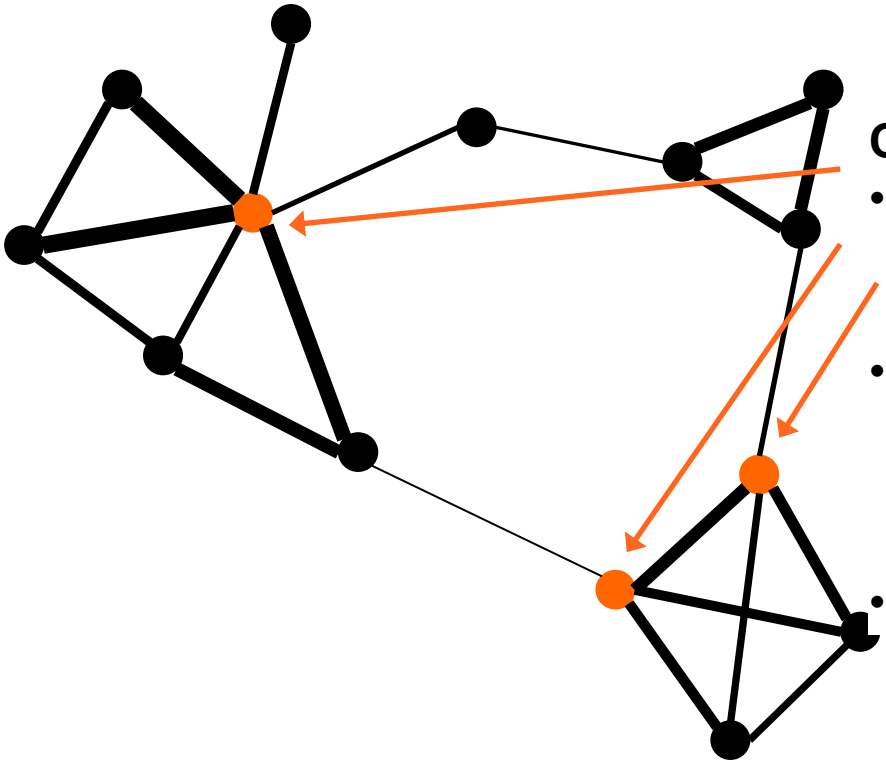
1. Define nodes (each one with a time series)
2. Define link weights (measures of time series similarity)
3. Define threshold, discard sub-threshold links

Functional networks: how-to?



Network from Nummenmaa et al. 2014, by permission

How do func brain networks look like?



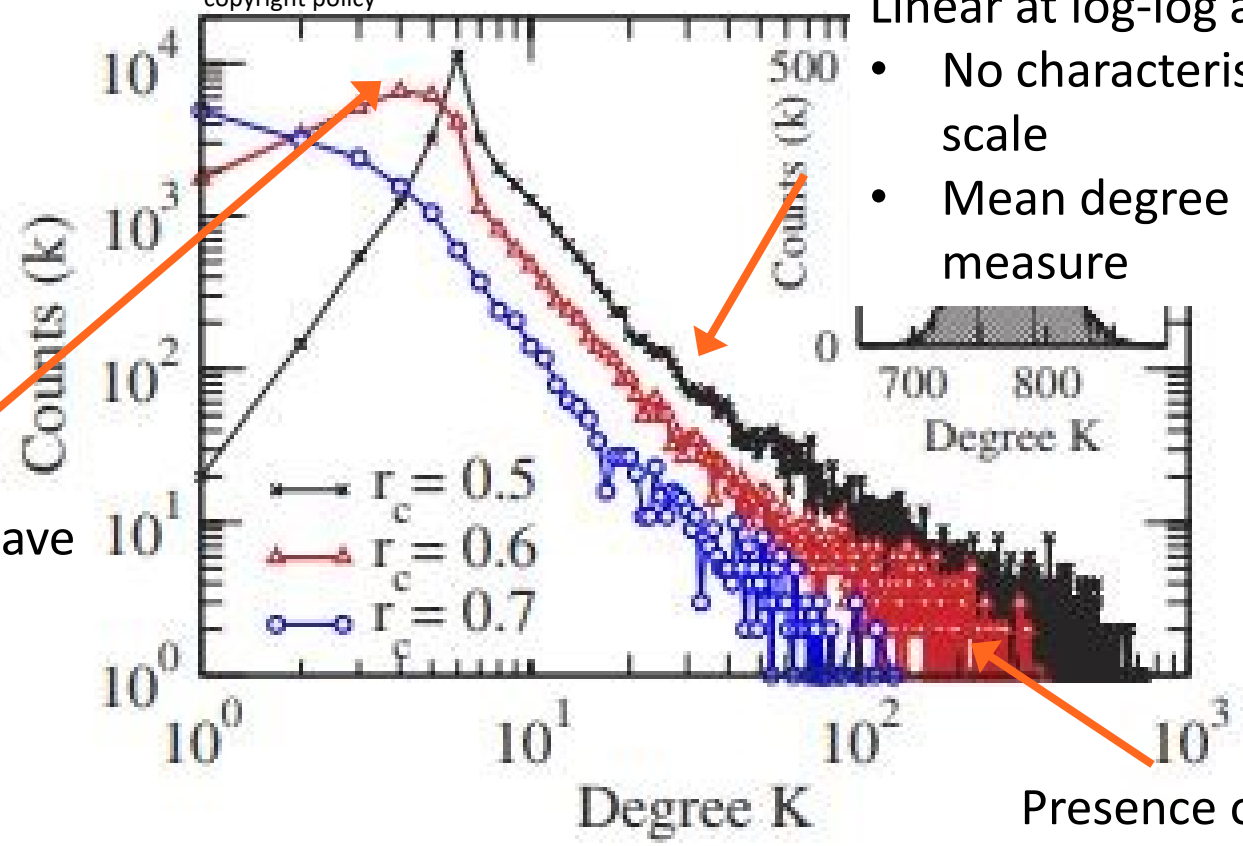
Centrality:

- 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)

Fig: Equíluz et al. 2005; lecture use allowed by the APS copyright policy



Linear at log-log axes:

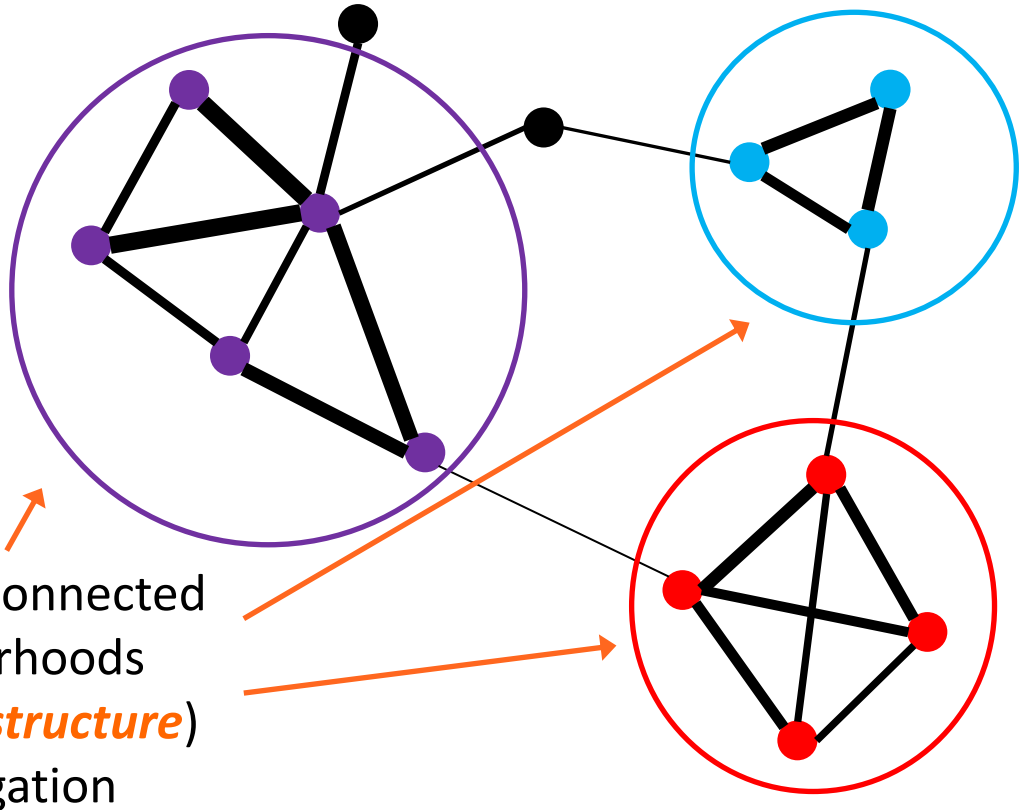
- No characteristic degree scale
- Mean degree a difficult measure

Most nodes have small degree

Presence of high-degree nodes = **hubs**

How do func brain networks look like?

Segregation-integration (Sporns 2013)

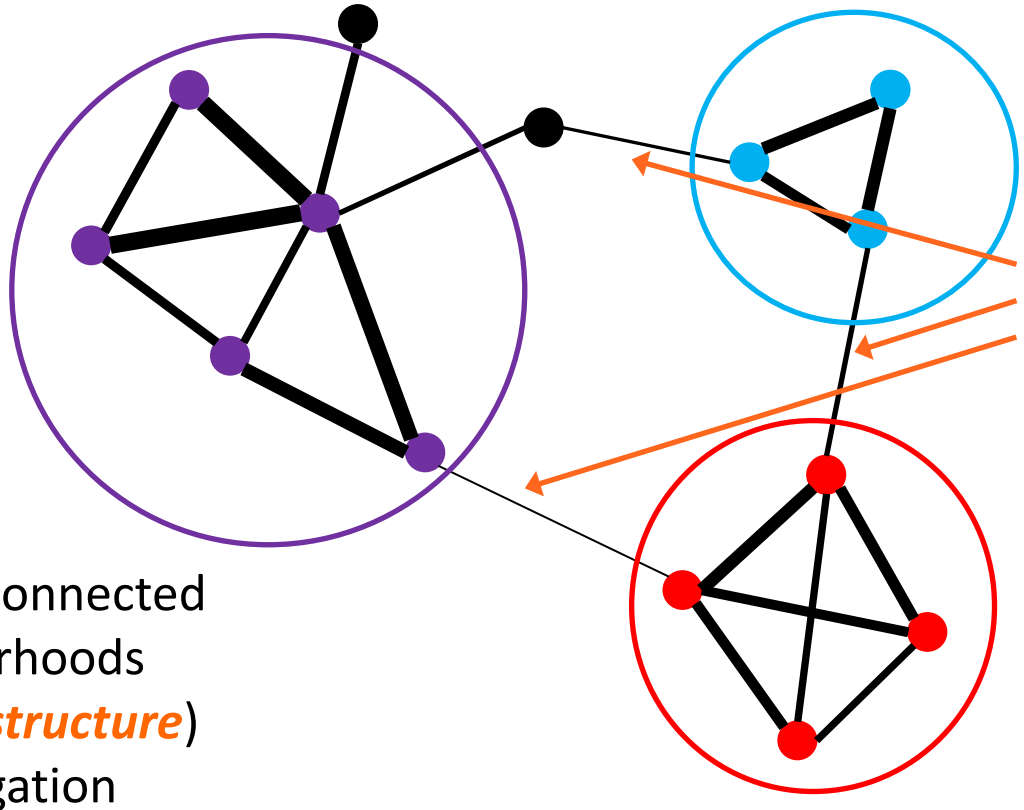


Strongly connected neighbourhoods (***module structure***)

- Segregation
- Functional specialization

How do func brain networks look like?

Segregation-integration (Sporns 2013)



Weaker links between modules

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

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

- Segregation
- Functional specialization

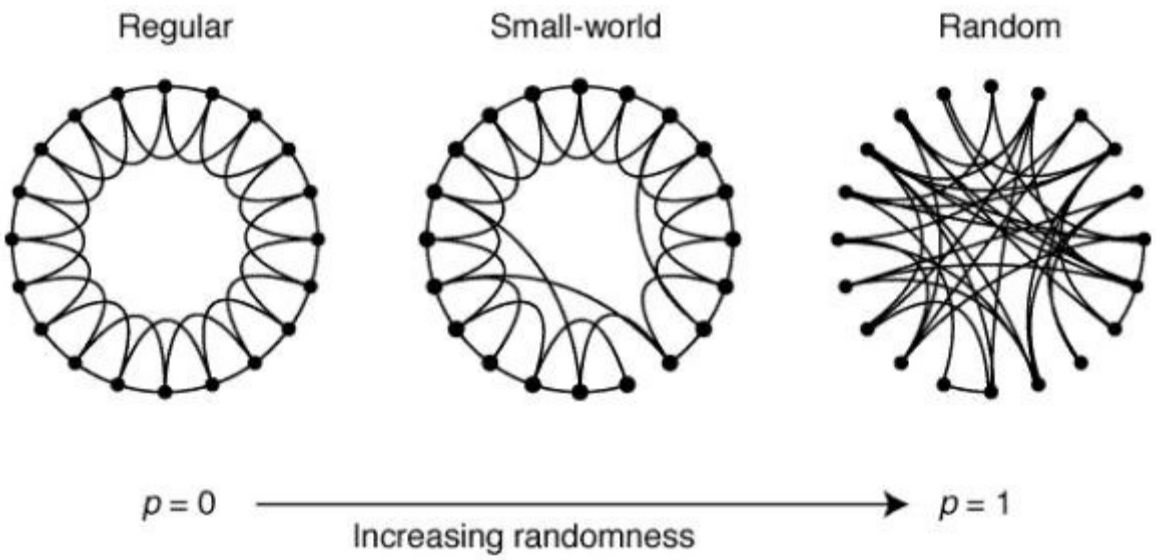
How do func brain networks look like?

Small-worldness

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

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

Fig: Watts & Strogatz 1998



Compared to random networks:

- High clustering (”friends of my friends are my friends”)
- Similar shortest path lengt

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?

Compared to random networks:

- High clustering (”friends of my friends are my friends”)
- Similar shortest path lengt

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

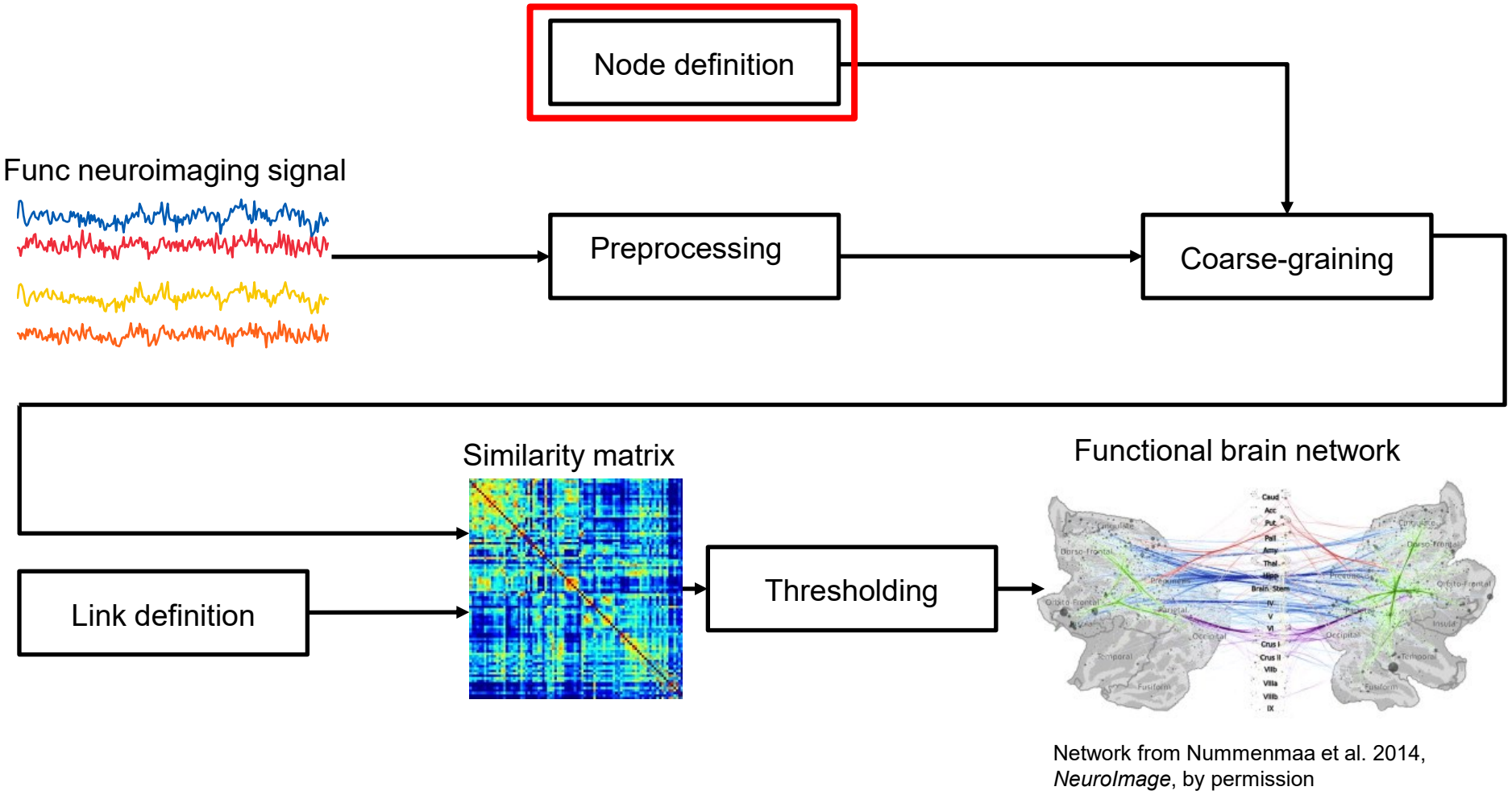
=> Natural assumption: brain networks change in time

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 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

More on this:

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

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?

How correlated are voxels of a ROI?

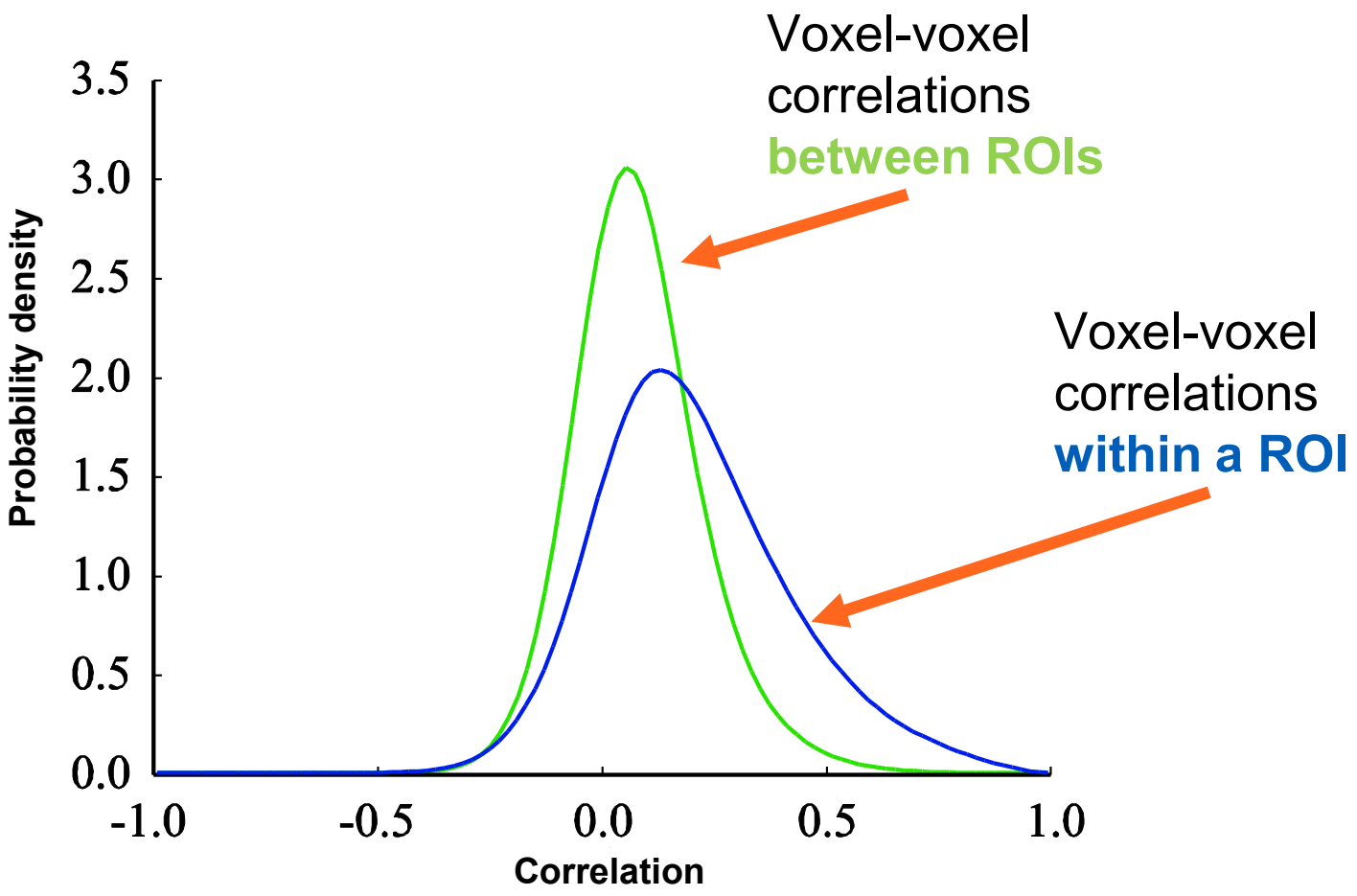


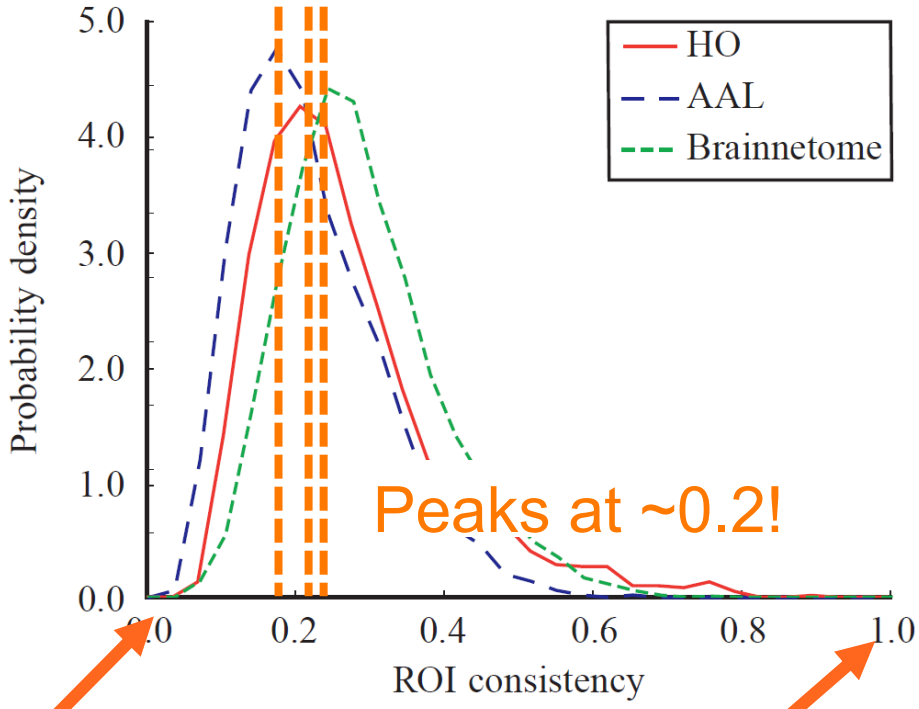
Fig: Korhonen et al. 2017

How homogeneous are ROIs?

Spatial consistency
= measure of functional homogeneity:

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

Fig: Korhonen et al. 2017



Lack of homogeneity

Perfect homogeneity

ROIs have rich internal connectivity structure

High spatial consistency

Low spatial consistency

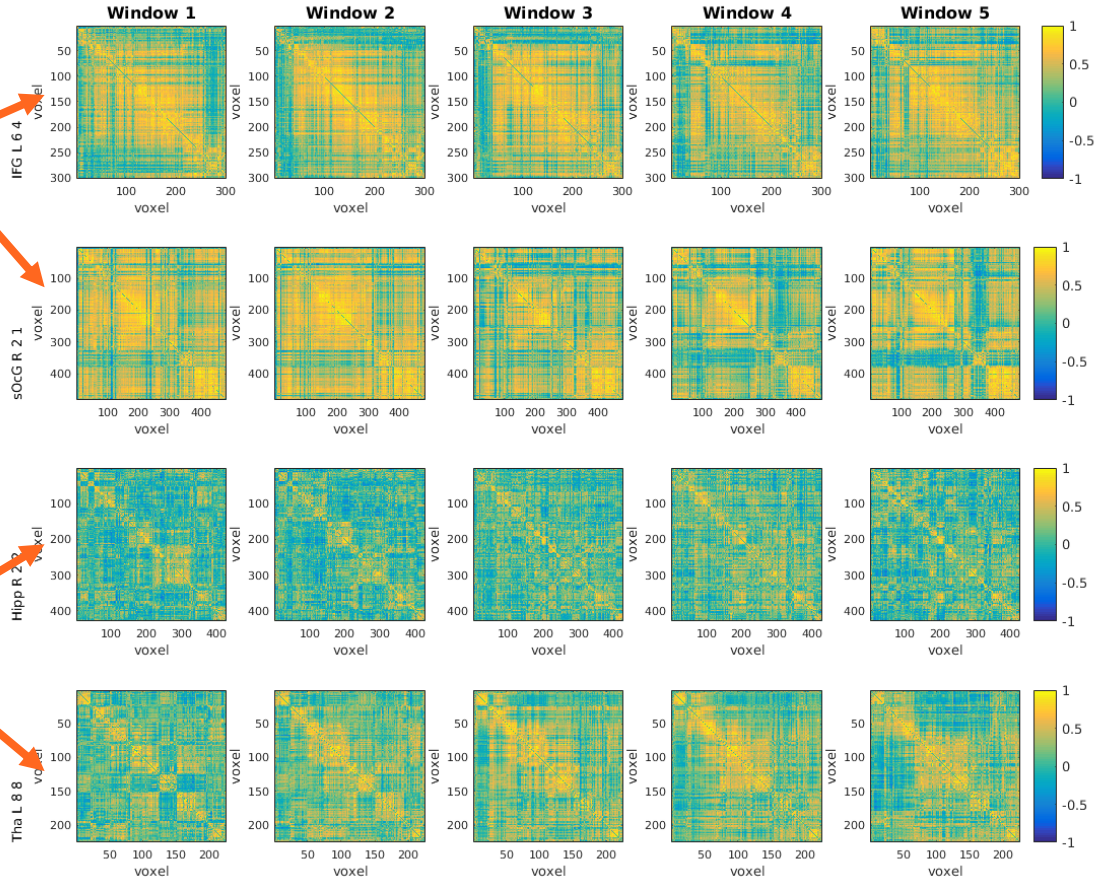


Fig: Ryyppö et al. 2018

ROIs have rich internal connectivity structure

High spatial consistency

Low spatial consistency

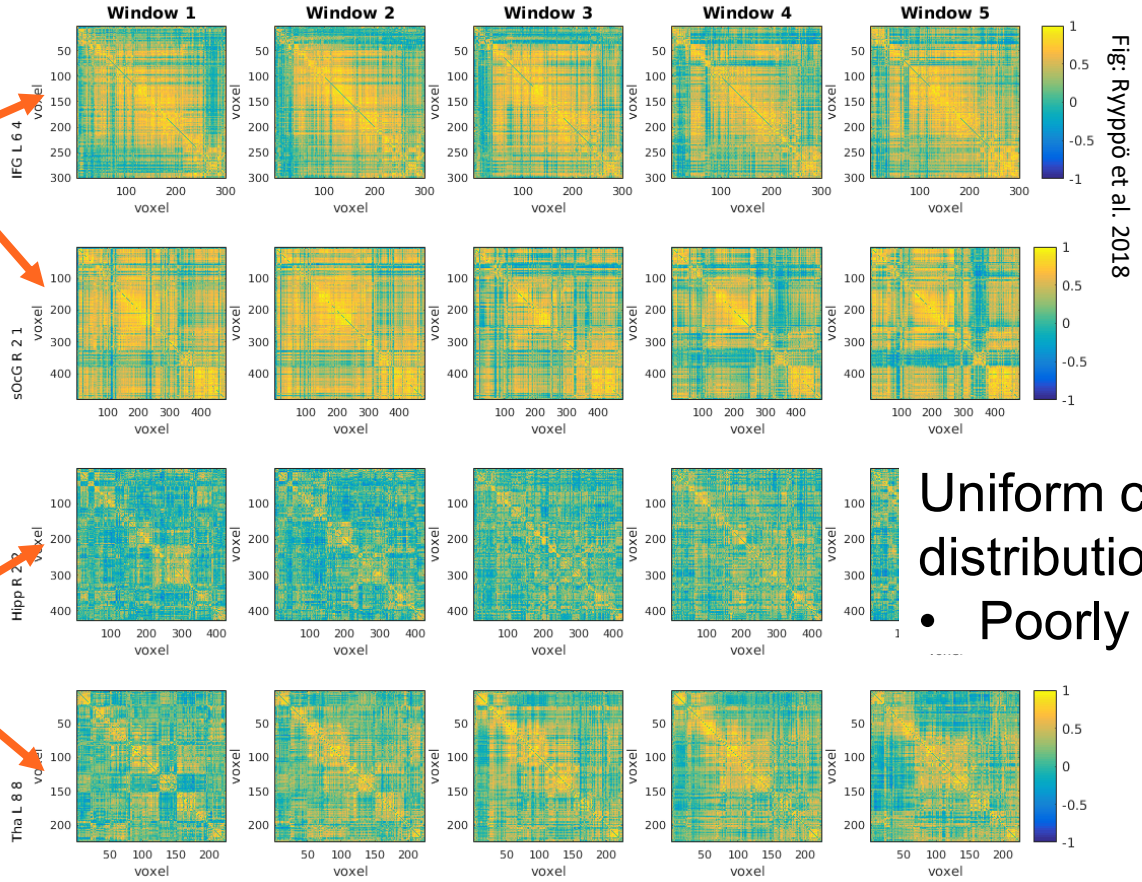


Fig: Ryyppö et al. 2018

Uniform correlation distribution

- Poorly defined ROI?

ROIs have rich internal connectivity structure

High spatial consistency

Low spatial consistency

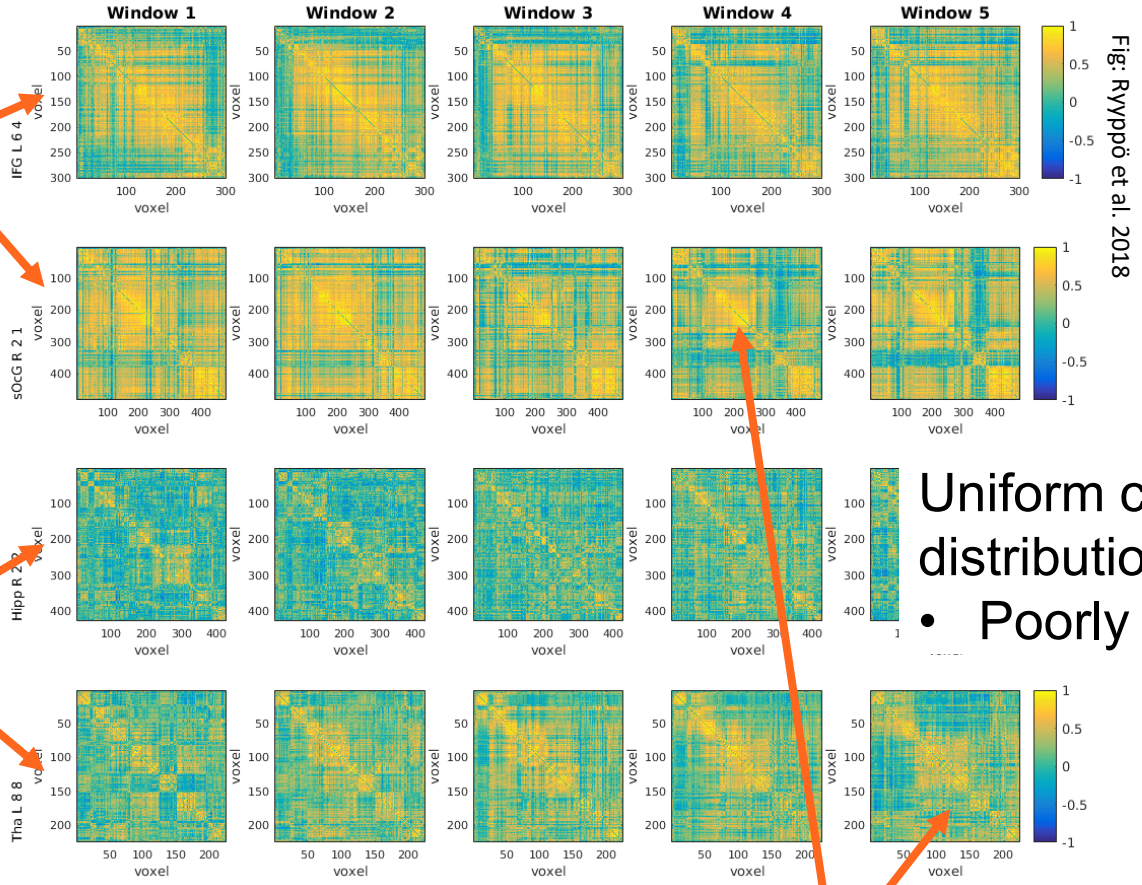


Fig: Ryyppö et al. 2018

Uniform correlation distribution

- Poorly defined ROI?

Intra-ROI modules

- Activation?
- Network topology?

ROIs have rich internal connectivity structure

High spatial consistency

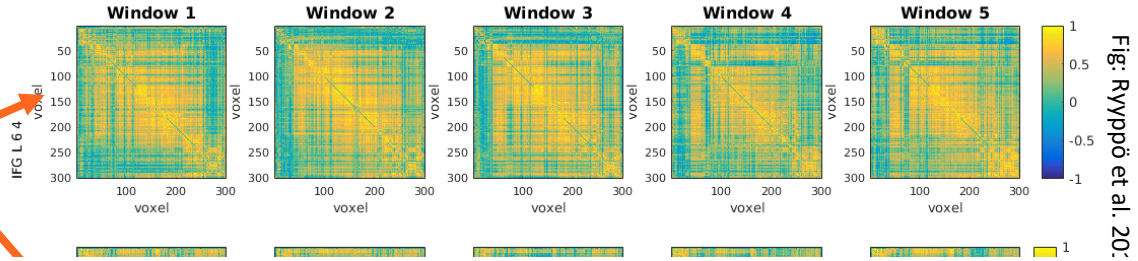


Fig: Ryyppö et al. 20

Ignored by current network construction pipelines!

Low spatial consistency

Uniform correlation distribution

- Poorly defined ROI?

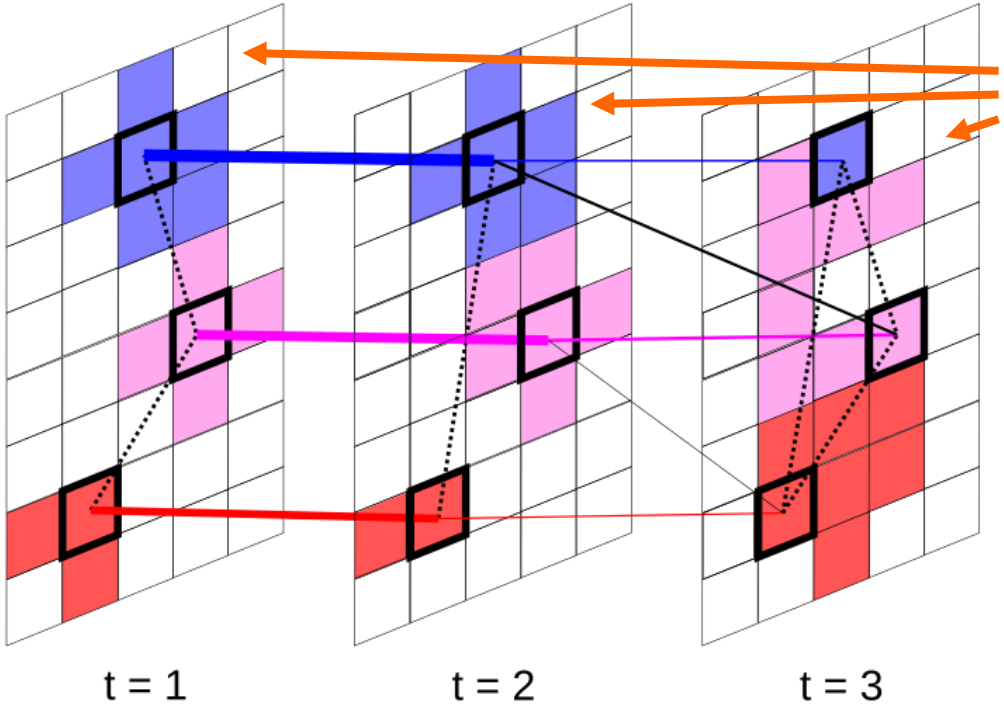
Intra-ROI modules

- Activation?
- Network topology?

Possible solution: time-dependent nodes

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

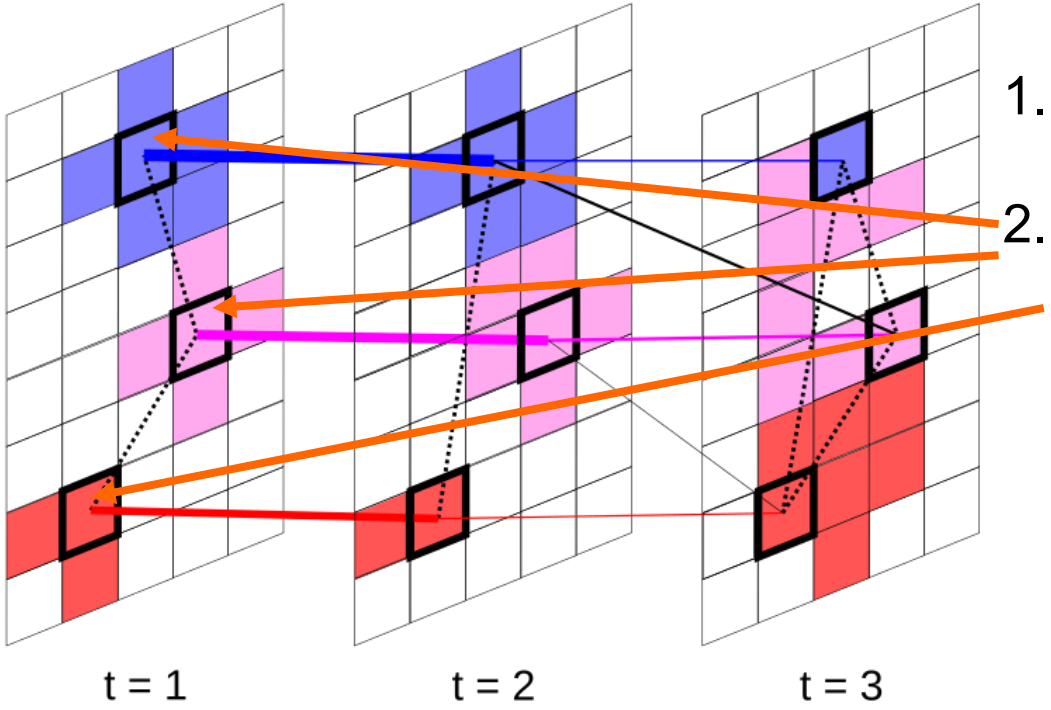
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



1. Layers = time windows

Possible solution: time-dependent nodes

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

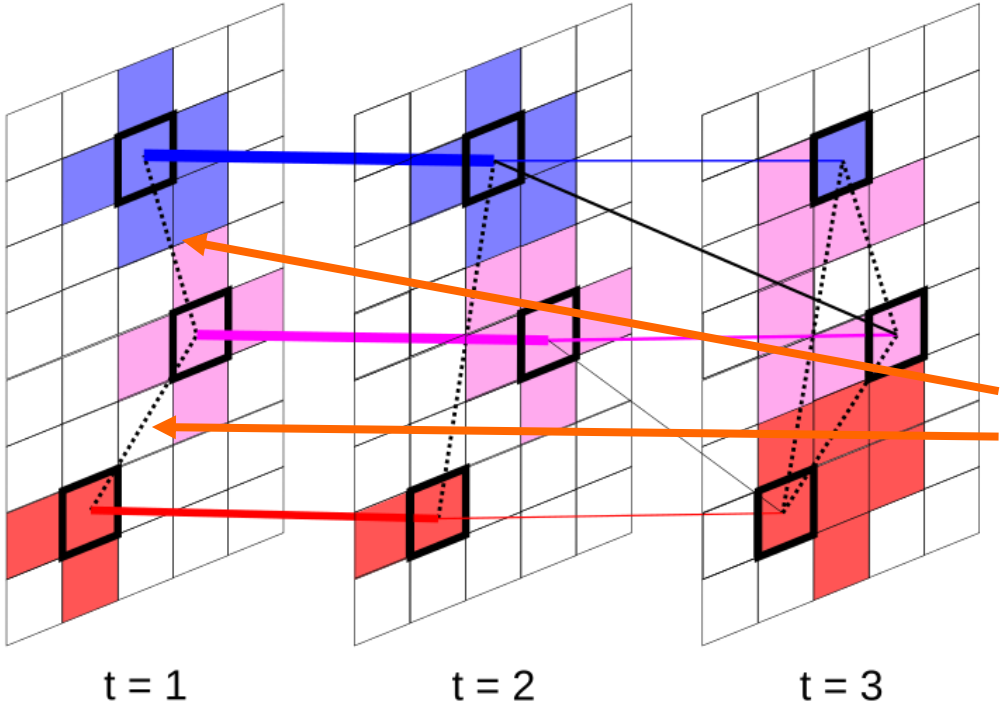


1. Layers = time windows

2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)

Possible solution: time-dependent nodes

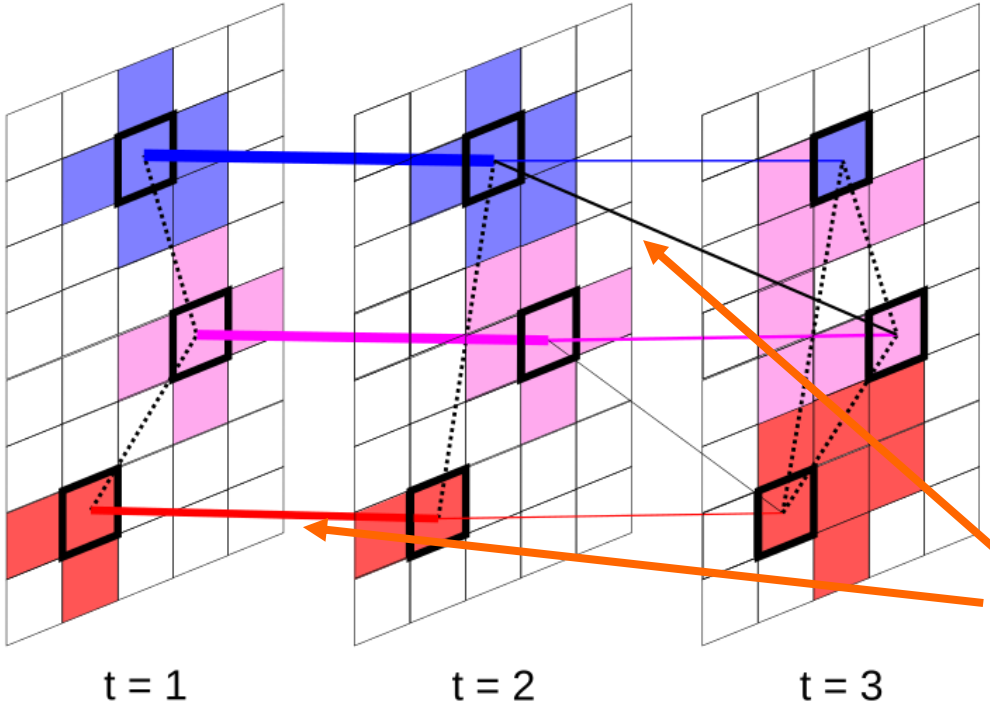
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



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

Possible solution: time-dependent nodes

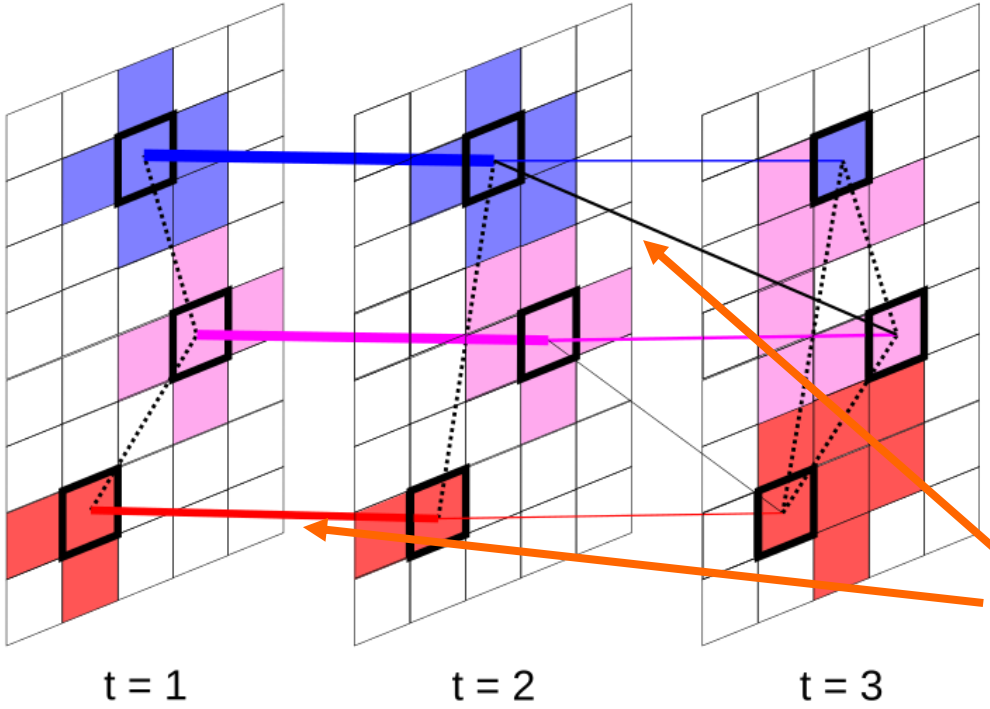
Based on multilayer networks (= different connections in the same network), for review: Kivelä et al. 2014



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**

References

Alakörkkö, T., Saarimäki, H., Glerean, E., Saramäki, J., & Korhonen, O. 2017. Effects of spatial smoothing on functional brain networks. *European Journal of Neuroscience* 46(9).

Bassett, D. S. & Sporns, O. 2017. Network Neuroscience. *Nature Neuroscience* 20(3).

de Santos-Sierra, D., Sendiña-Nadal, I., Leyva, I., Almendral, J. A., Anava, S., Ayali, A., Papo, D., & Boccaletti, S. 2014. Emergence of small-world anatomical networks in self-organizing clustered neuronal cultures. *PLoS One* 9(1): e85828.

Equíluz, V. M., Chialvo, D. R., Cecchi, G. A., Baliki, M., & Apkarian, A. V. 2005. Scale-free brain functional networks. *Physical Review Letters* 94.

Granovetter, M. S. 1973. The strength of weak ties. *American Journal of Sociology* 78(6).

Hagmann, P. 2005. *From diffusion MRI to brain connectomics*. Lausanne: Ecole Politechnique Fédérale de Lausanne (EPFL) (Doctoral dissertation).

Iraji, A., Deramus, T. P., Lewis, N., Yaesoubi, M., Stephen, J. M., Erhard, E., …, Calhoun, V. D. 2019. The spatial chronnectome reveals a dynamic interplay between functional segregation and integration. *Human Brain Mapping* 40(10).

Kivelä, M., Arenas, A., Barthelemy, M., Gleeson, J. P., Moreno, Y., & Porter, M. A. 2014. Multilayer networks. *Journal of Complex Networks* 2(3).

Korhonen, O., Saarimäki, H., Glerean, E., Sams, M., & Saramäki, J. 2017. Consistency of Regions of Interest as nodes of fMRI functional brain networks. *Network Neuroscience* 1(3).

Korhonen, O., Zanin, M., Papo, D., 2021. Principles and open questions in functional brain network reconstruction. *Human Brain Mapping* 42(11).

Muldoon, S. F. & Bassett, D. S. 2016. Network and multilayer network approaches to understanding human brain dynamics. *Philosophy of Science* 82(5).

Nummenmaa, L., Saarimäki, H., Glerean, E., Gostopoulos, A., Jääskeläinen, I. P., Hari, R., & Sams, M. 2014. Emotional speech synchronizes brains across listeners and engages large-scale dynamic brain networks. *NeuroImage* 102.

Papo, D., Zanin, M., Martínez, J. H., & Buldú, J. M. 2016. Beware of the small-world neuroscientist! *Frontiers in Human Neuroscience* 10.

Ryyppö, E., Glerean, E., Brattico, E., Saramäki, J., & Korhonen, O. 2018. Regions of Interest as nodes of dynamic functional brain networks. *Network Neuroscience* 2(4)

Sporns, O & Zwi, J. D. 2004. The small world of the cerebral cortex. *Neuroinformatics* 2(2).

Sporns, O., Tononi, G., & Götter, R. 2005. The human connectome: A structural description of the human brain. *PLoS Computational Biology* 1(4): e42.

Sporns, O. 2013. Network attributes of segregtation and integration in the human brain. *Current Opinion in Neurobiology* 23(2).

Wang, J., Wang, L., Zang, Y., Yang, H., Tang, H., Gong, Q., … He, Y. 2009. Parcellation-dependent small-world brain functional networks: A resting-state fMRI study. *Human Brain Mapping* 30(5).

Watts, D. J. & Strogatz, S. H. 1998. Collective dynamics of ”small-world” networks. *Nature* 393.

White, J. G., Southgate, E., Thompson, J. N., & Brenner, S. 1986. The structure of the nervous system of the nematode *Caenorhabditis elegans*: The mind of a worm. *Philisophical Transactions of the Royal Society B* 134.

Zalesky, A., Fornito, A., & Bullmore, E. 2012. On the use of correlation as a measure of network connectivity. *NeuroImage* 60(4).

Thank you!

Questions, comments?

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Slides: github.com/onerva-korhonen/presentations/blob/master/CNA_krakow_170723.pdf