How <u>not</u> to construct functional brain networks

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IFISC, Palma de Mallorca

26.10.2022

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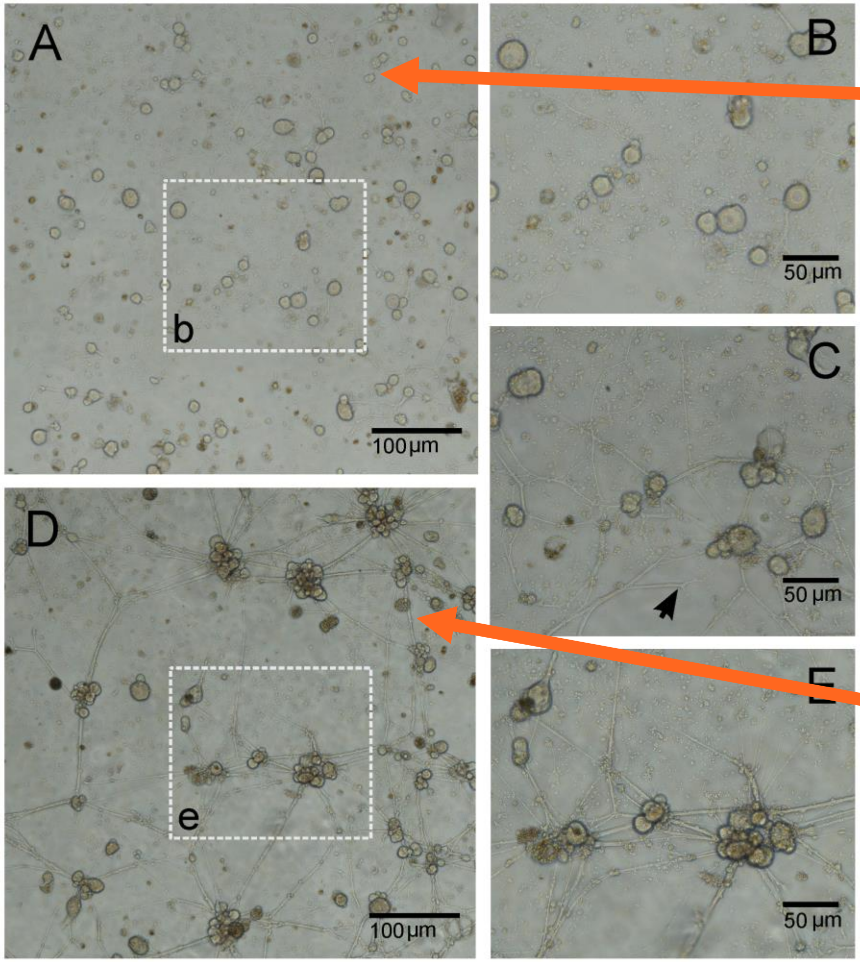
SUOMEN AKATEMIA
FINLANDS AKADEMI
ACADEMY OF FINLAND

Slides: https://github.com/onerva-korhonen/presentations/blob/master/ifisc_261022.pdf

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

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

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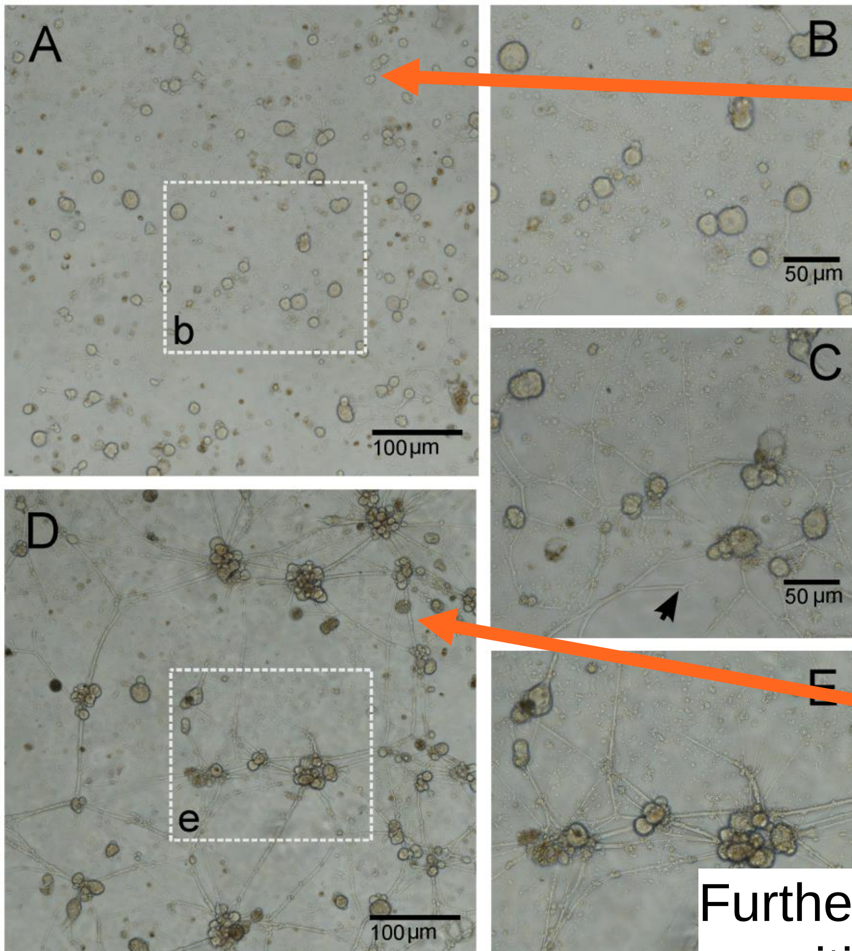


Fig: de Santos-Sierra et al. 2014, published under CC BY 4

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

Network neuroscience

(Bassett & Muldoon 2016, Bassett & Sporns 2017)

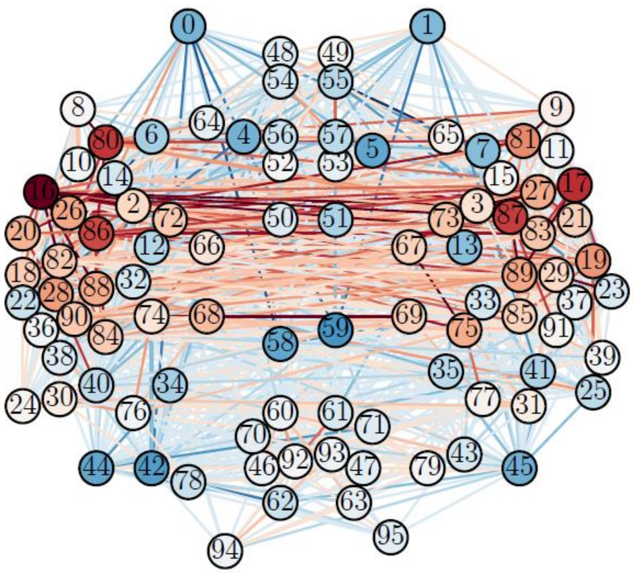


Fig: Alakörkkö *et al*. 2017, *European Journal of Neuroscience*

- Network neuroscience = applying network tools on the brain
- Two aims:
  1. Understand the healthy brain
  2. Find causes of diseases

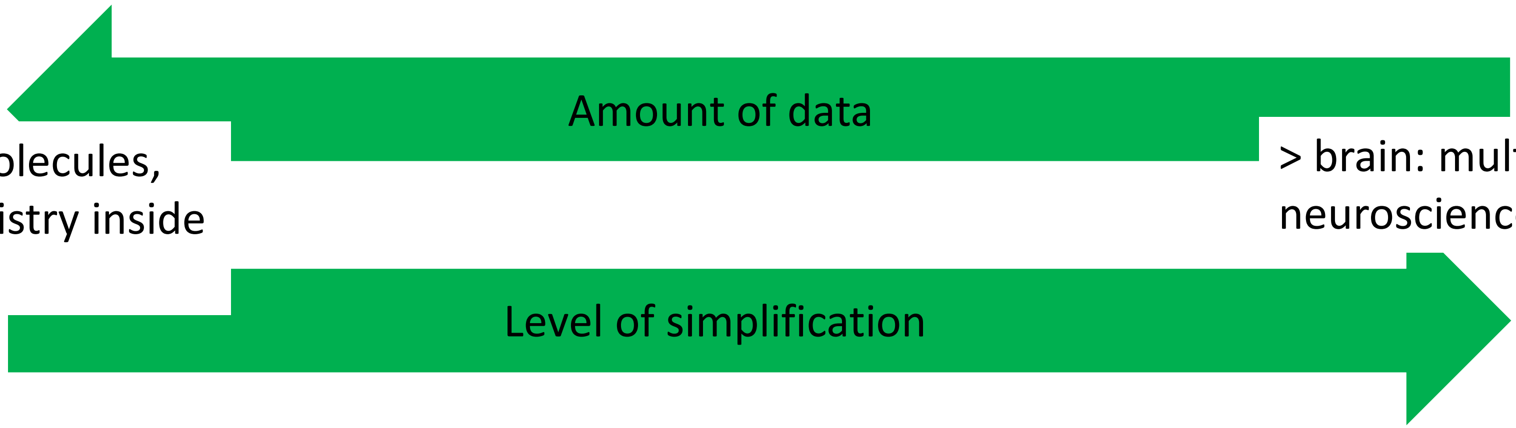
Scales of net neurosci

Cell level: 10^{11} neurons, 10^{14} synapses

Mesoscopic level: 10^4 datapoints

Macroscopic level: 100 brain areas

< cell: molecules, biochemistry inside cells



> brain: multiperson neuroscience

Animal models:
C. Elegans: 302 neurons

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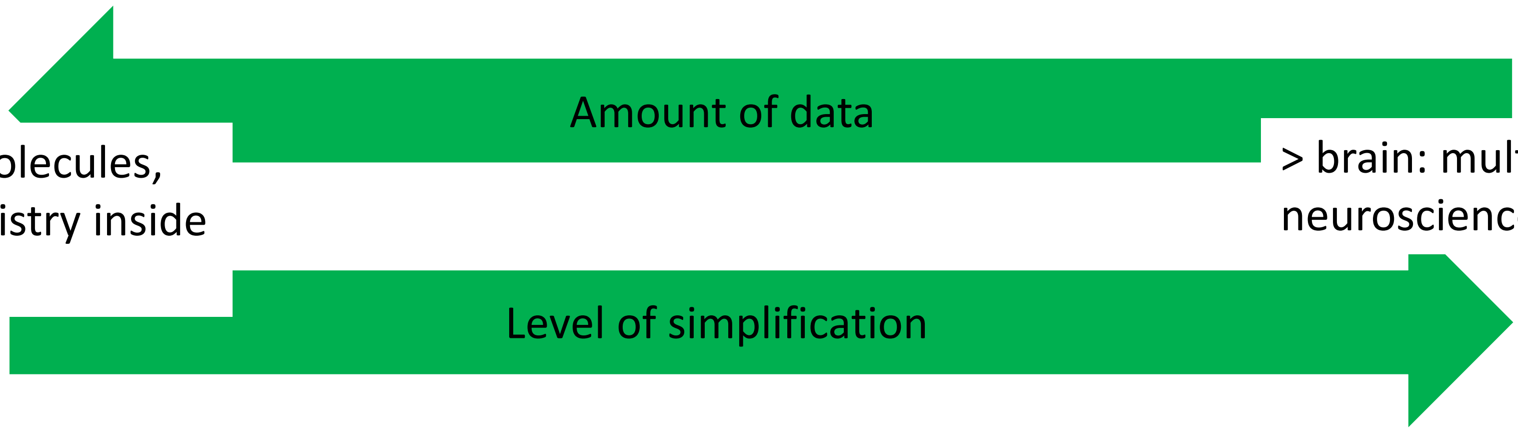

> brain: multiperson neuroscience

Animal models:
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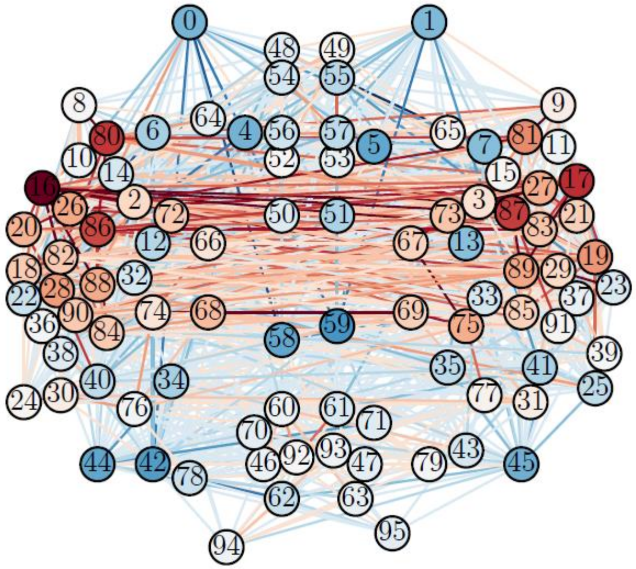
+ **temporal scales:** milliseconds (neuronal communication)
hours (within and between tasks)
months (e.g. learning)
years (human lifespan)

Network neuroscience



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(Bassett & Muldoon 2016, Bassett & Sporns 2017)

- 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

Functional magnetic resonance imaging (= fMRI)

Fig: Aalto Magnetic Imaging (AMI Center), by permission

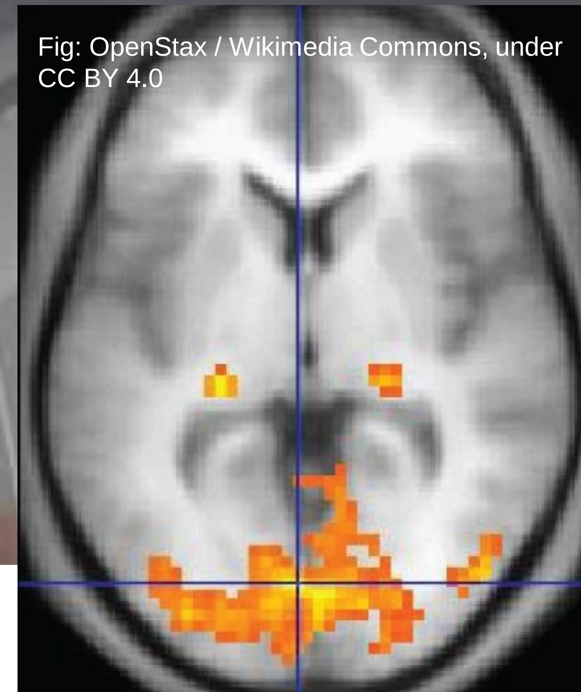
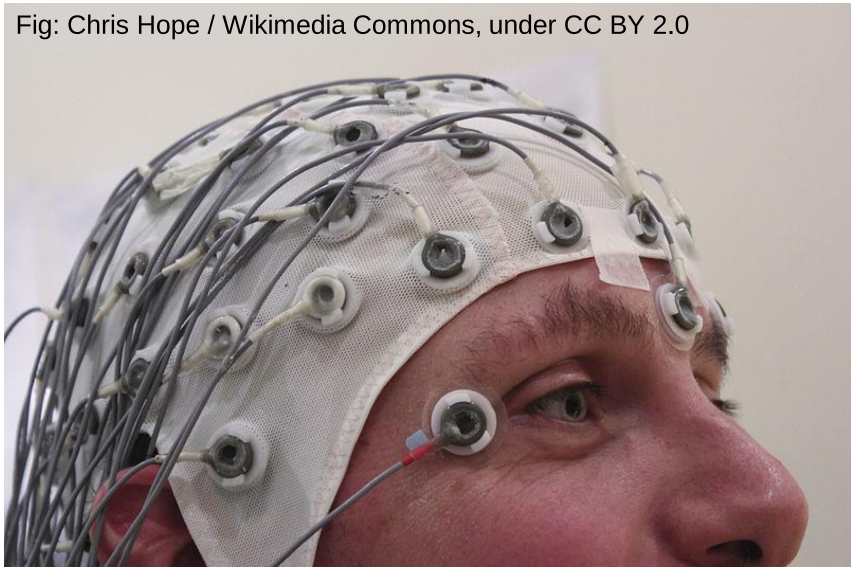


Fig: OpenStax / Wikimedia Commons, under CC BY 4.0

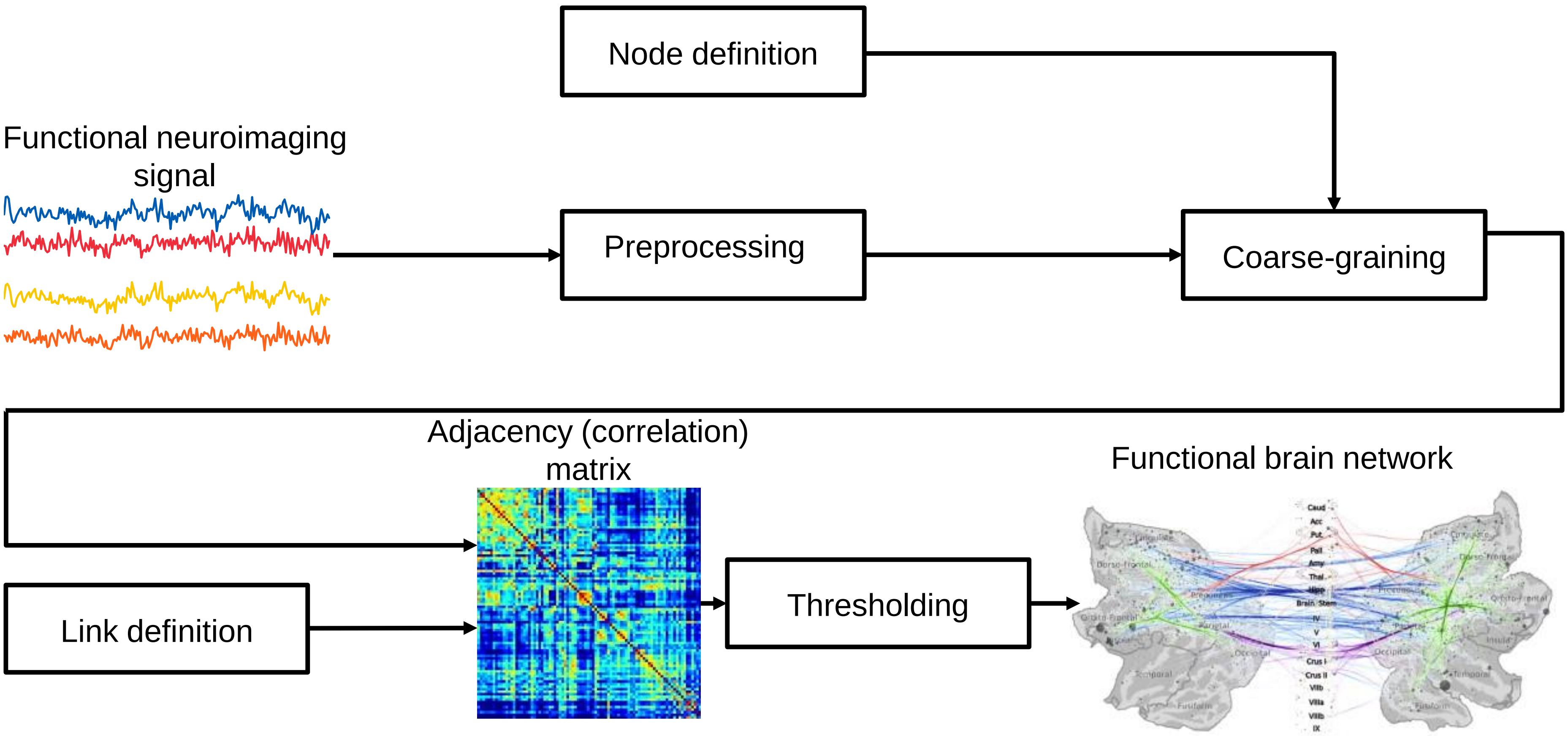
- Based on magnetic properties of haemoglobin
- fMRI uses two magnetic fields:
  1. A strong static field aligns haemoglobin molecule spins
  2. A short pulse disturbes the alignment
- After the pulse, spins return to equilibrium, emitting a radio wave
- Different waves from oxygen-rich and oxygen-poor heamoglobin
  => **oxygen-rich areas localized**
- Brain function requires oxygen
  => **high oxygen level = high activity** (indirect activity measure)
- Measurement unit = voxel
- Spatial resolution ~mm, temporal resolution ~s

Electroencephalograph (= EEG), magnetoencephalography (= MEG)



- Neurons interact electrically
- **EEG:** the electrical field of the brain
- **MEG:** the magnetic field of the brain
- Measurement unit = sensor
- Inverse model: time series of brain surface vertices
- Temporal resolution ~ ms, spatial resolution ?

Functional brain networks: how-to?



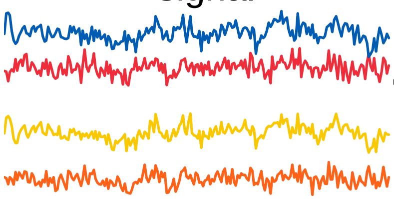
Network from Nummenmaa et al. 2014, *NeuroImage*, by permission

Functional brain networks: how-to?

Node definition

- Spatial smoothing (Alakörkkö et al. 2017, Triana et al. 2020)
- Standard space (ongoing with E. Rimmi)

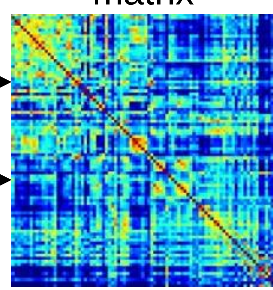
Functional neuroimaging signal



Preprocessing

Coarse-graining

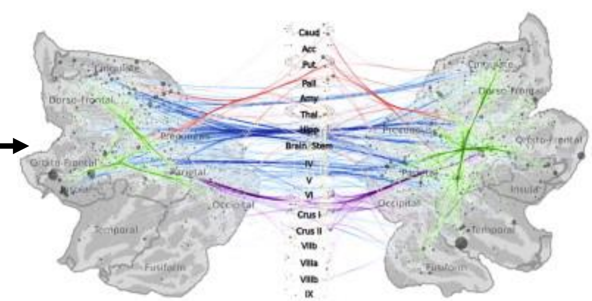
Adjacency (correlation) matrix



Link definition

Thresholding

Functional brain network



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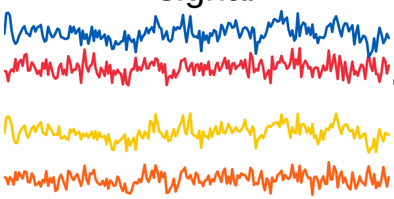

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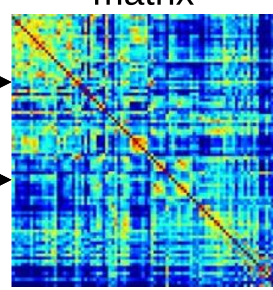

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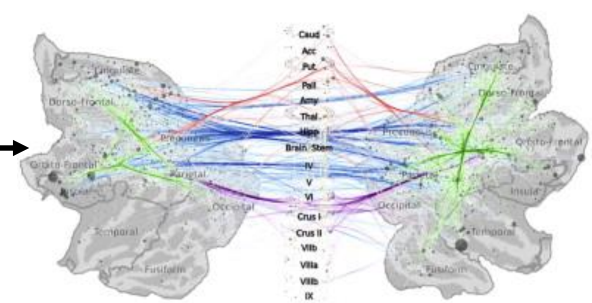
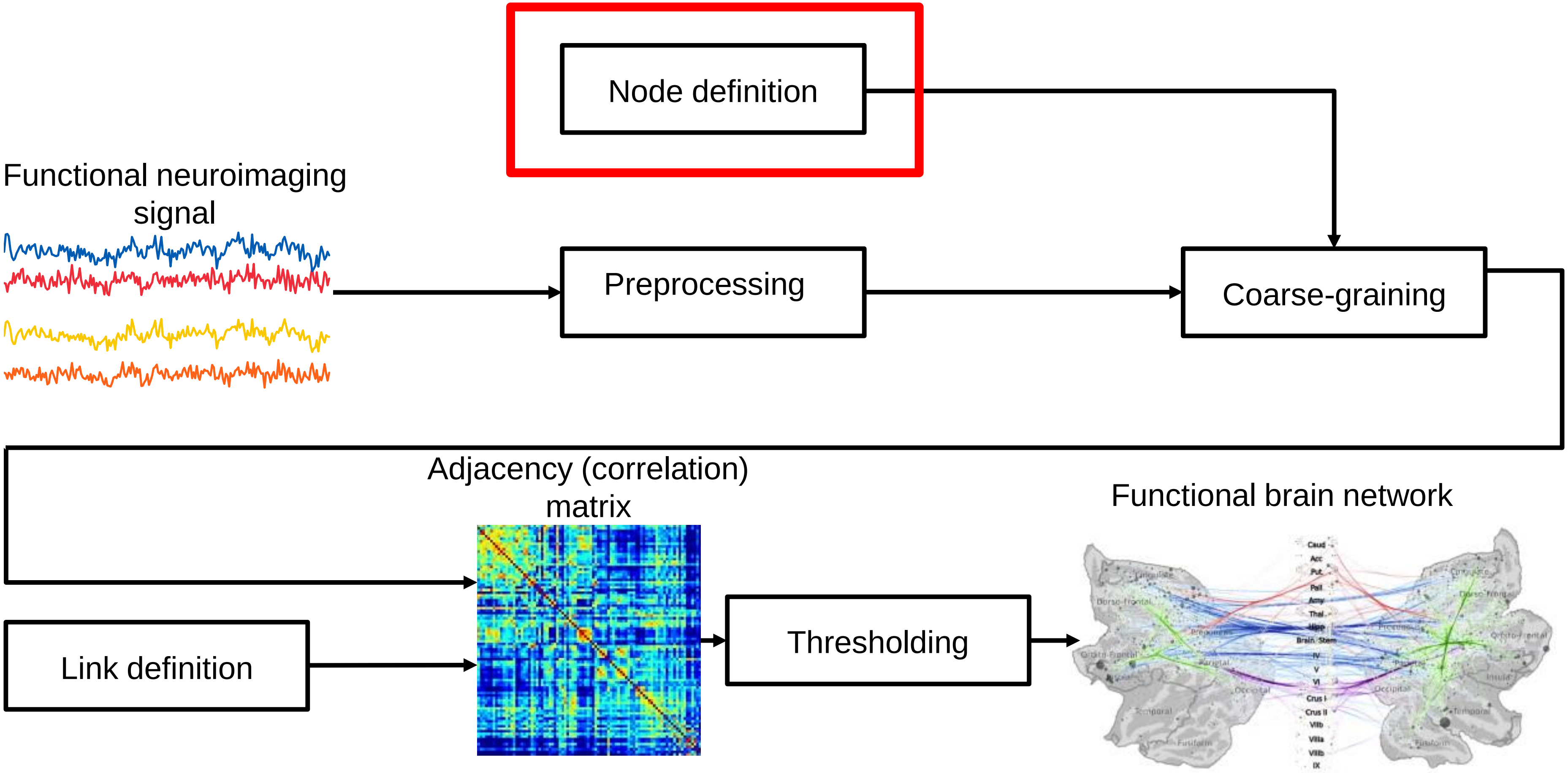


Network from Nummenmaa et al. 2014, *NeuroImage*, by permission

- Pearson correlation, partial correlation, other?
- Bayesian approaches (ongoing with Ivanoska, Zanin et al.)

Functional brain 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 are similar)?
- ROI time series to represent voxel dynamics:

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

More on this:

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

Violent?

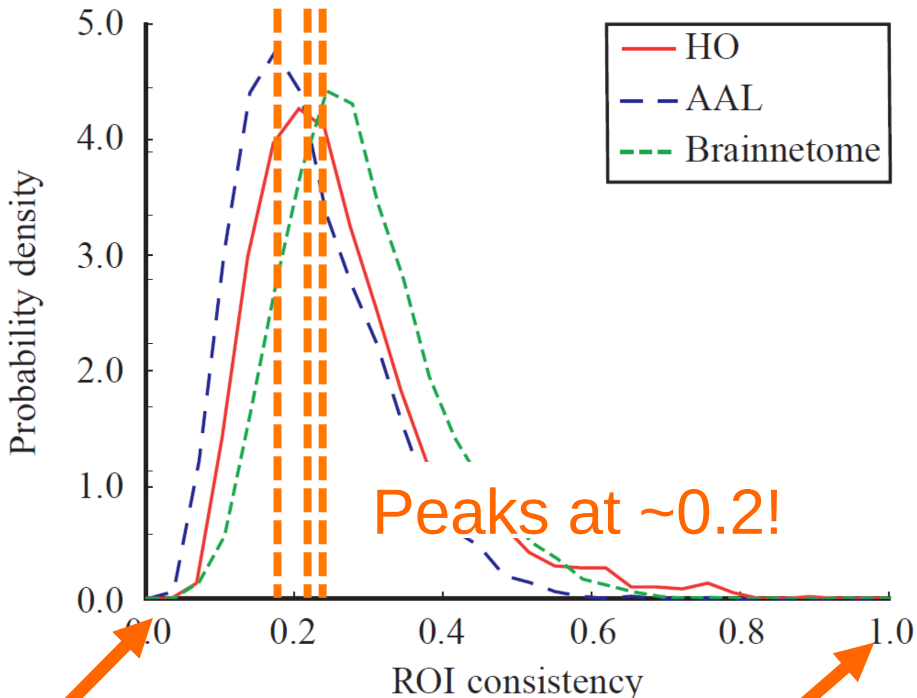
How homogeneous are ROIs?

Korhonen et al., 2017. *Network Neuroscience*

- ***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



Lack of homogeneity

Perfect homogeneity

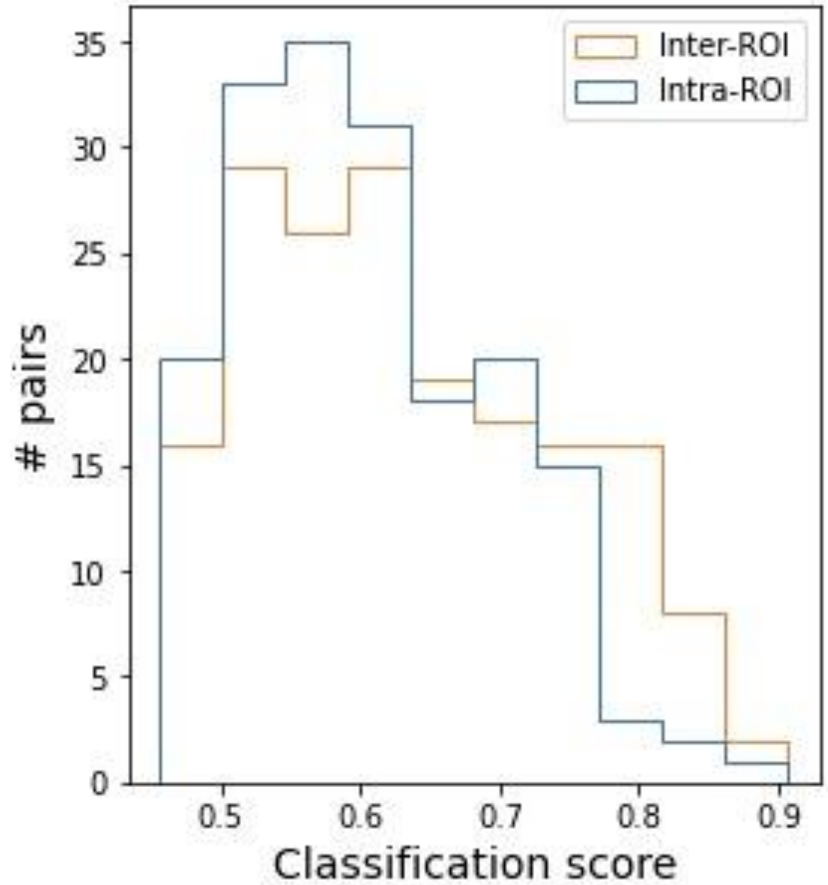
- Correlates with ROI size & connectivity

How homogeneous are ROIs?

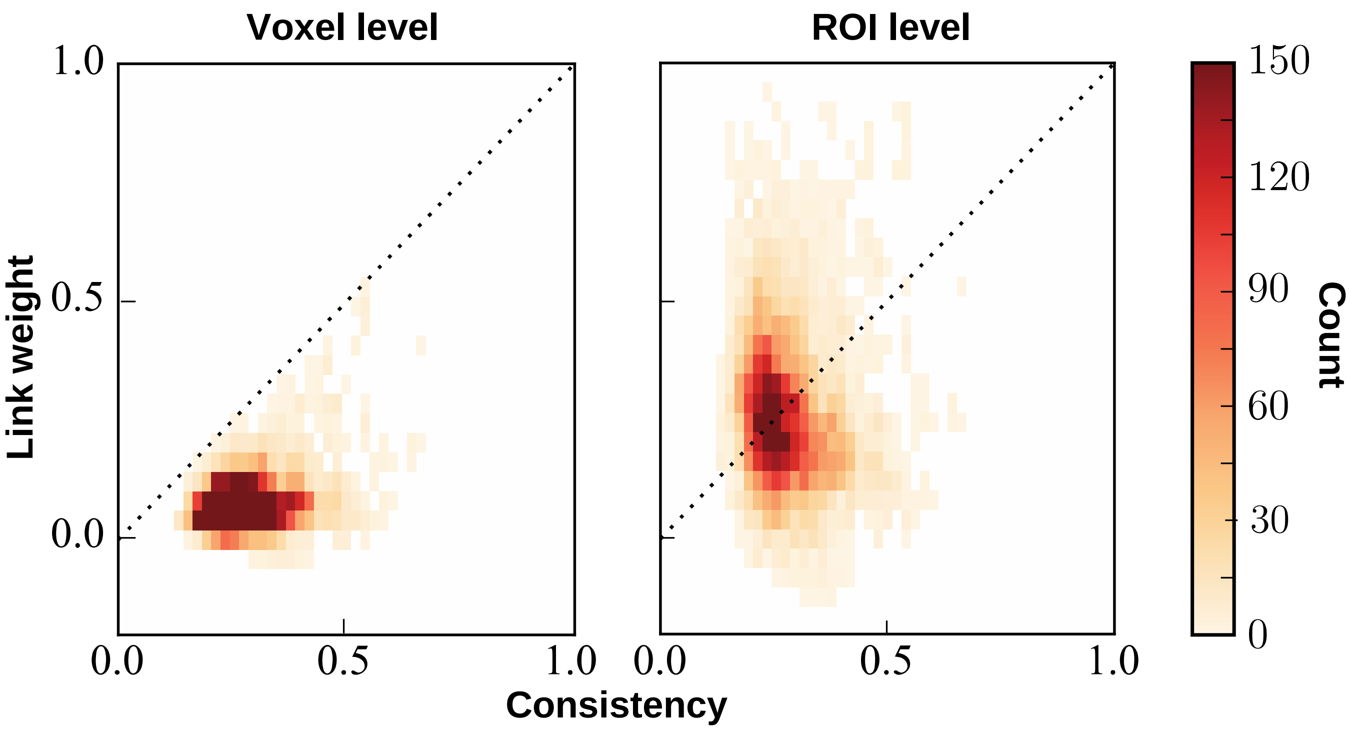
Latest news:
No nonlinear homogeneity in ROIs either!

- *Identifiability* (= recognisability for a deep learner) only marginally higher for voxel pairs in different than in same ROIs
- Ongoing with M. Zanin

Fig: M. Zanin (personal communication over secretary)

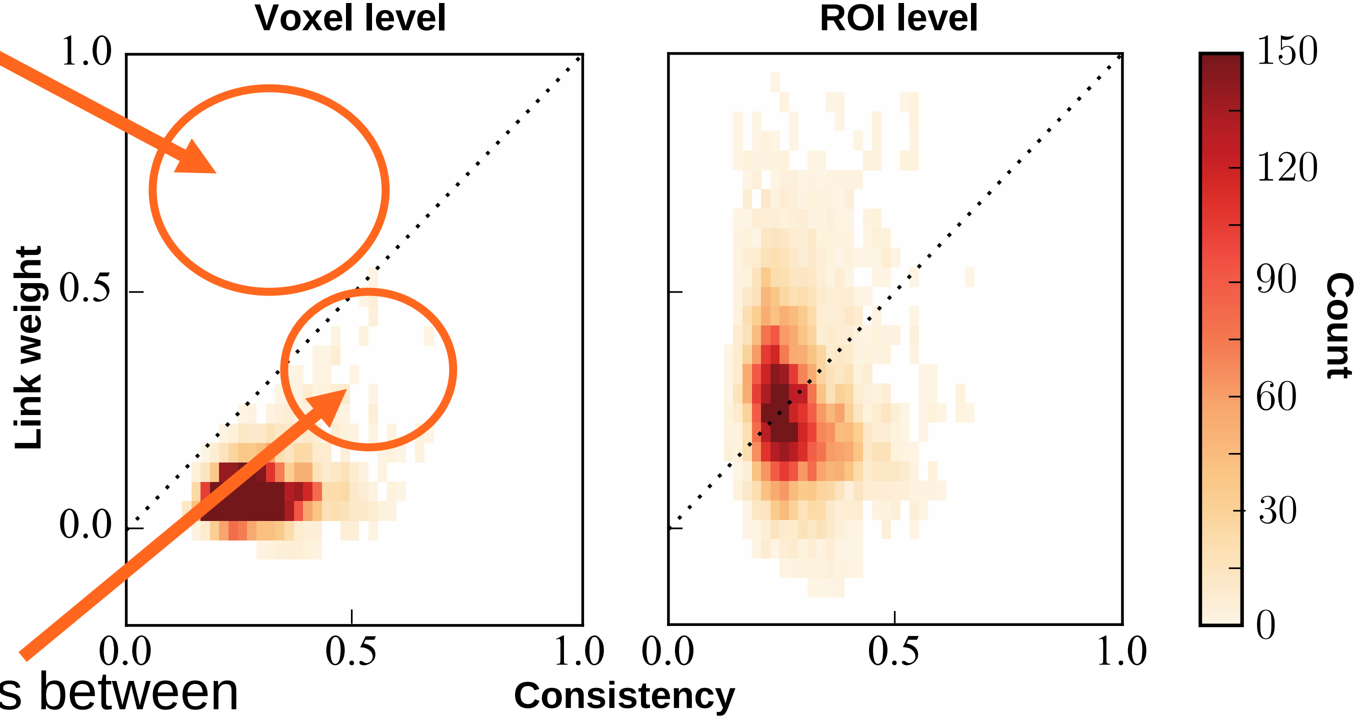


Does consistency predict connectivity?



Does consistency predict connectivity?

No links



Strong links between consistent ROIs

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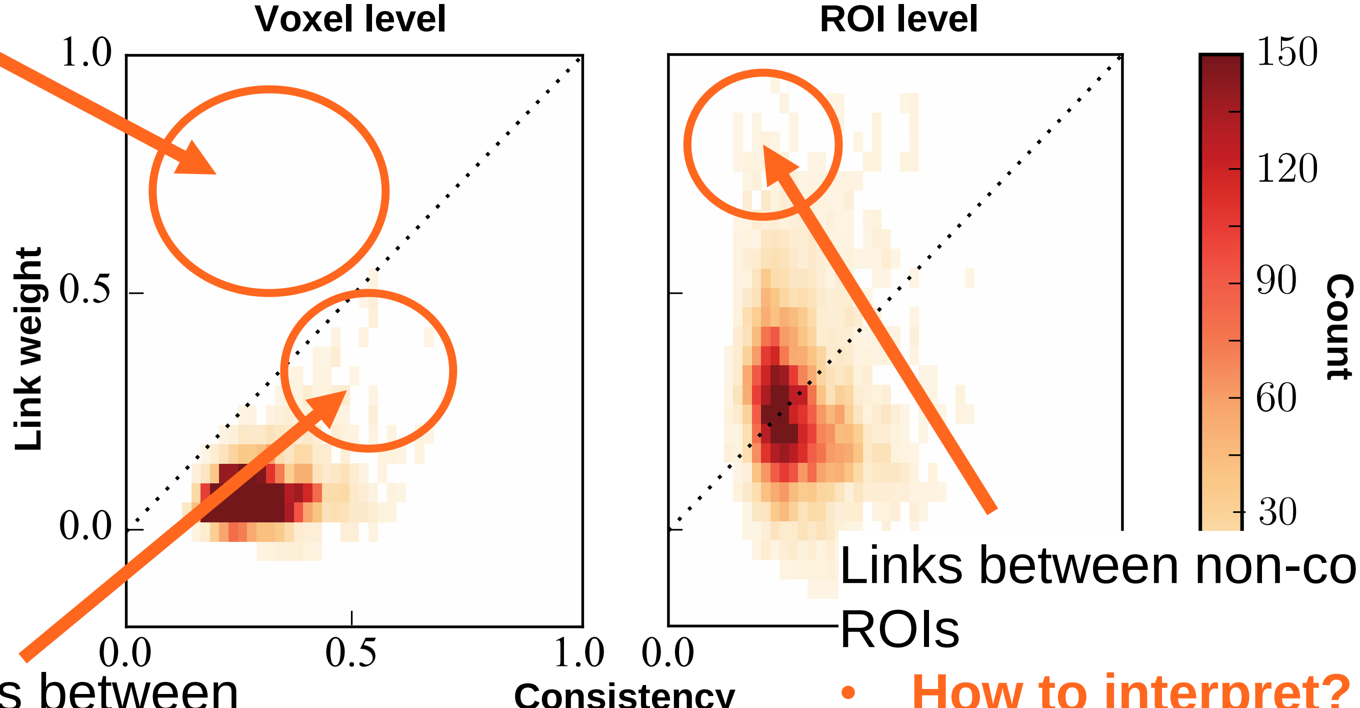
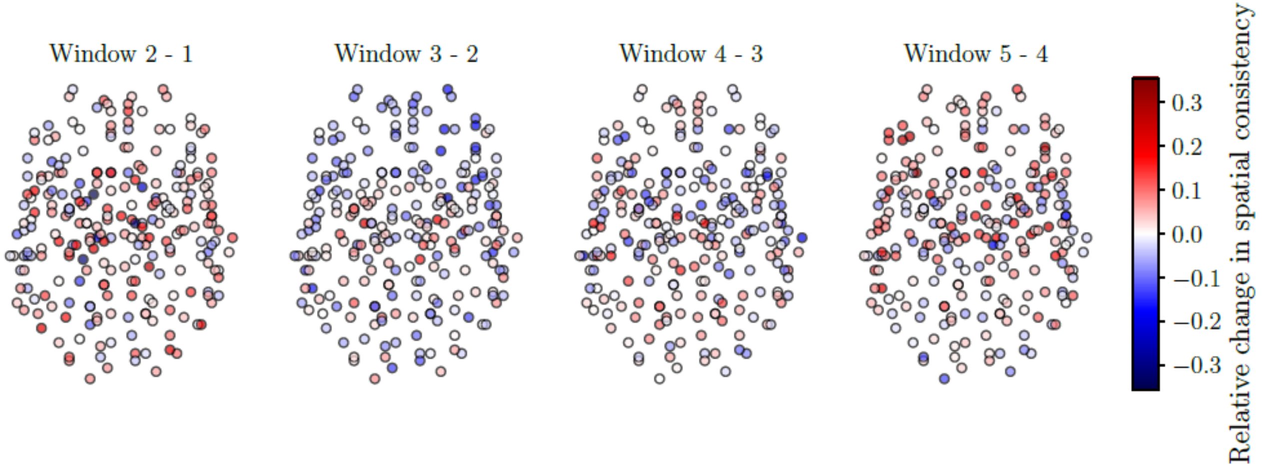


Strong links between consistent ROIs

Links between non-consistent ROIs

- **How to interpret?**

Spatial consistency changes in time



Ryyppö et al., 2018. *Network Neuroscience*

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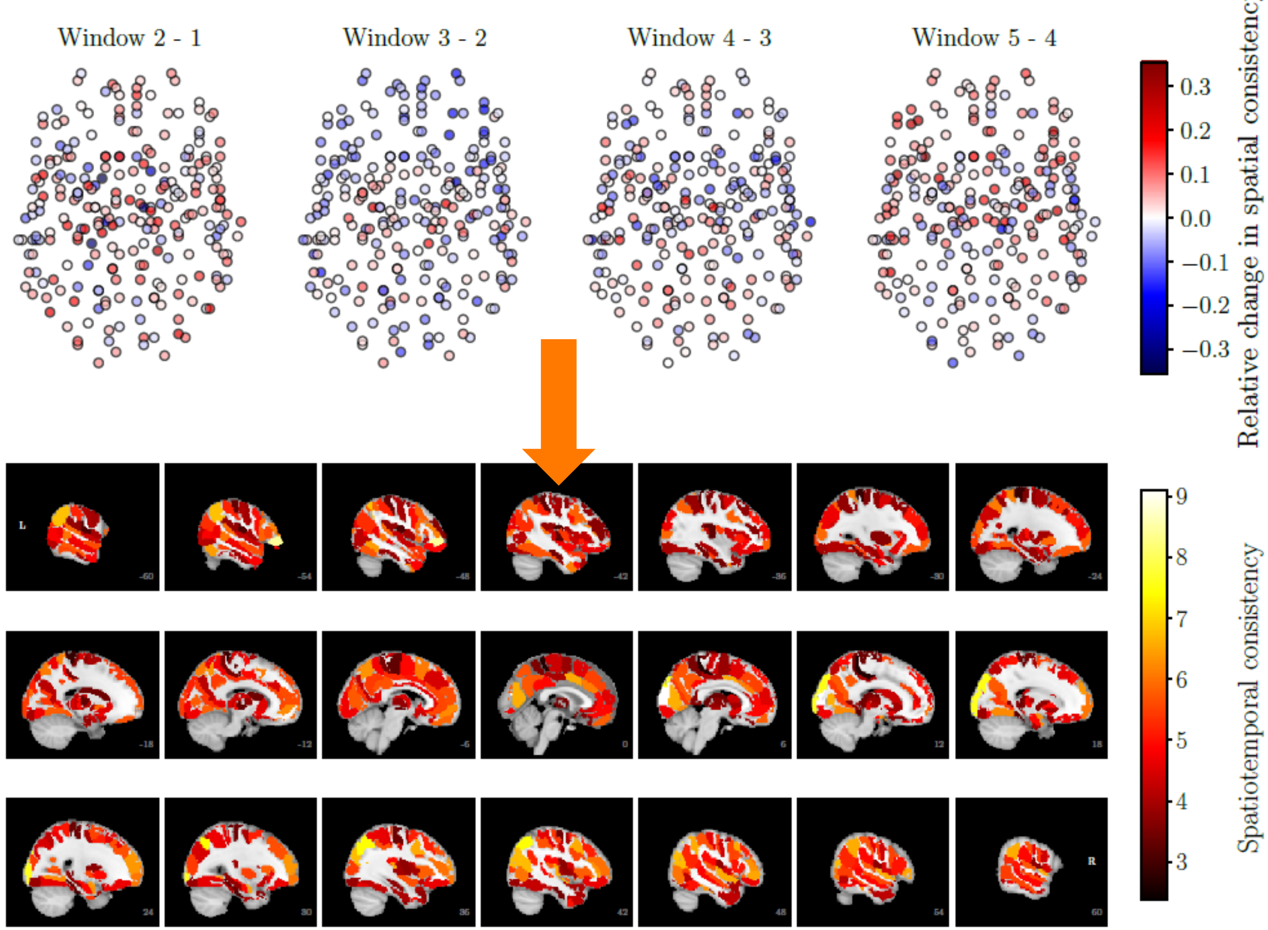

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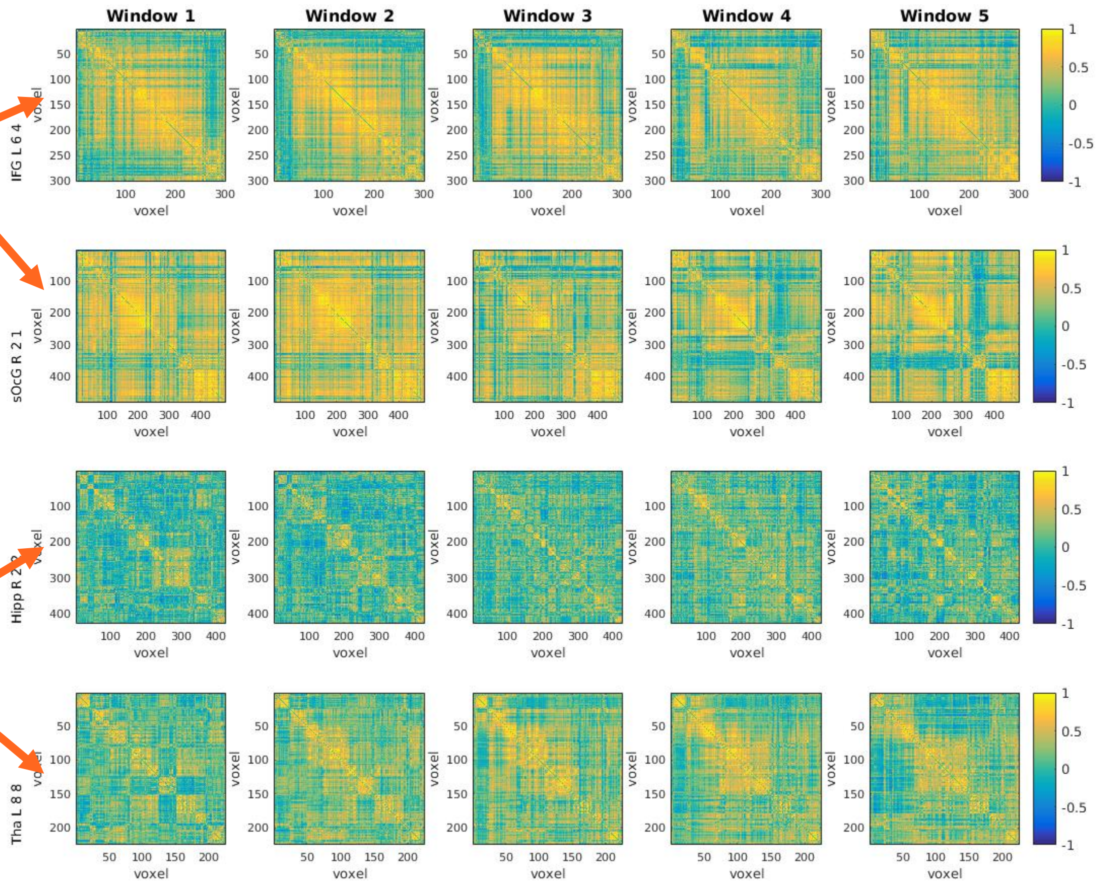
Spatiotemporal consistency

= stability of spat. consistency

ROIs have rich internal connectivity structure

High spatial consistency

Low spatial consistency



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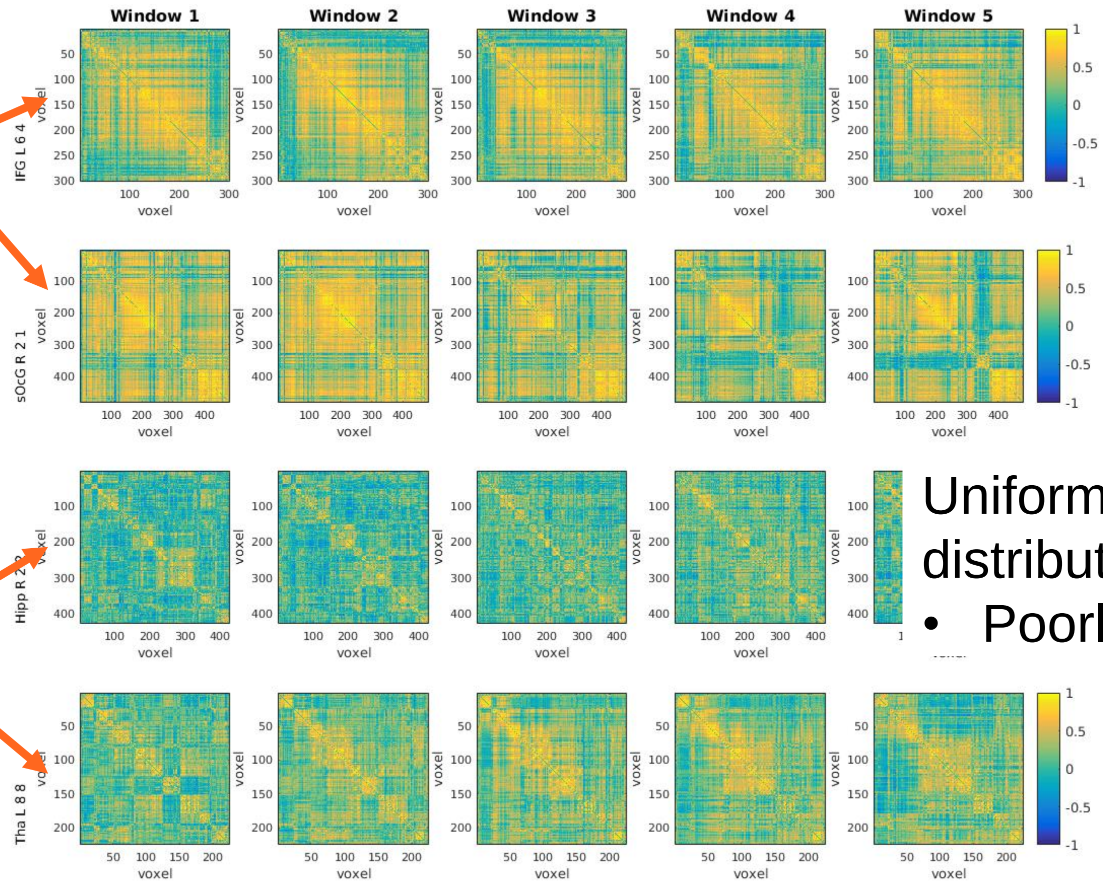

Uniform correlation distribution

- Poorly defined ROI?

Ryyppö et al., 2018. *Network Neuroscience*

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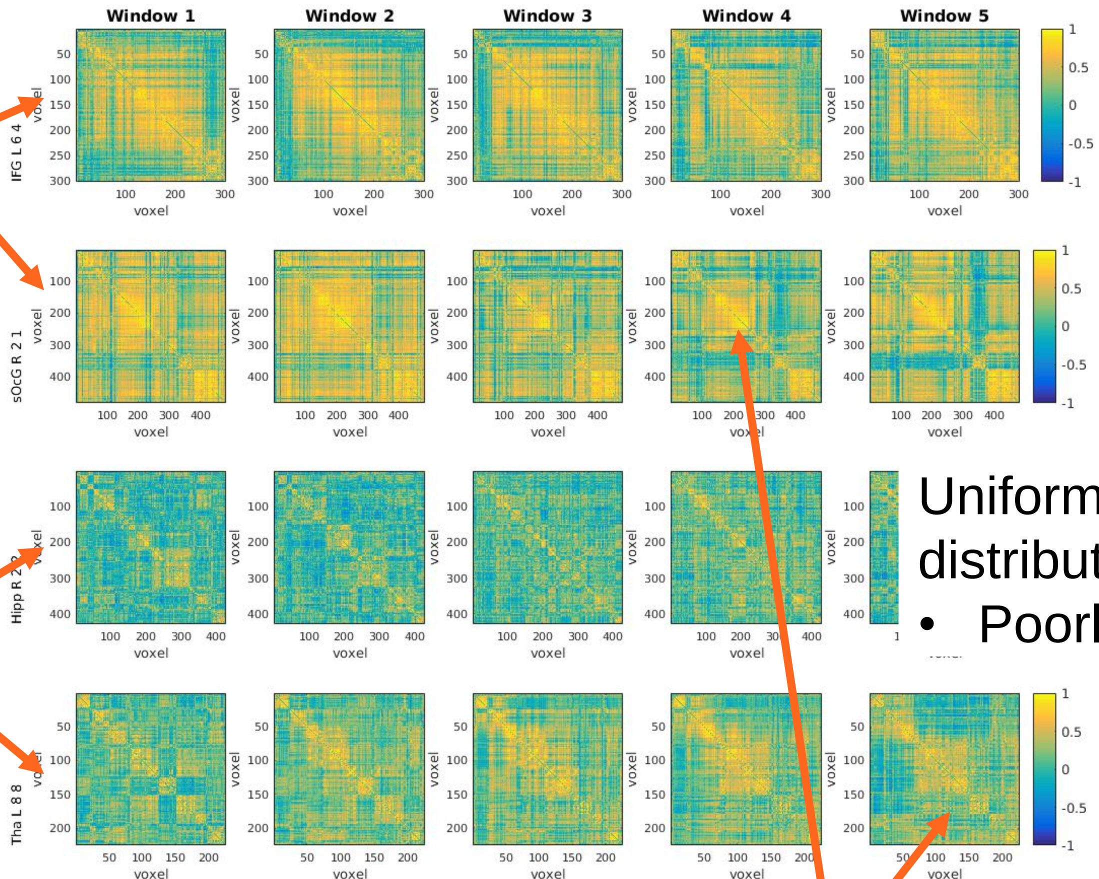


Ryyppö et al., 2018. *Network Neuroscience*

Uniform correlation distribution

- Poorly defined ROI?

Intra-ROI modules

- Network topology?

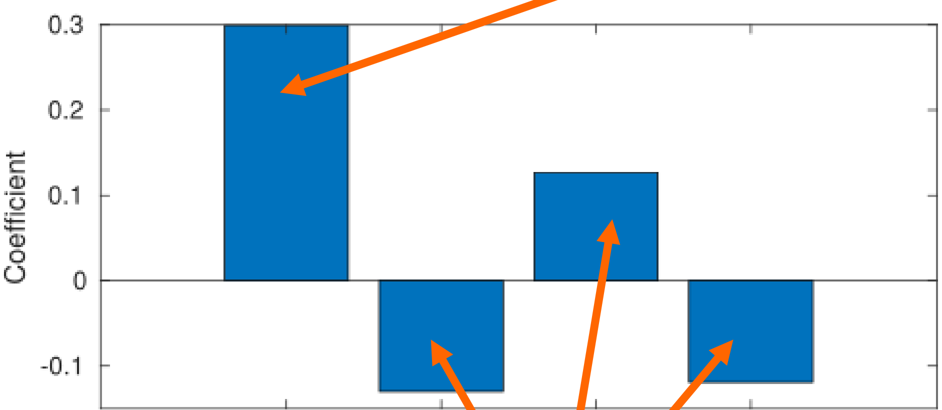
Consistency predicts topology

(ongoing with E. Ryyppö)

Hub vs non-hub:
Accuracy:
Training 60.39%
Test 60.23%
(> Random 50.03%)

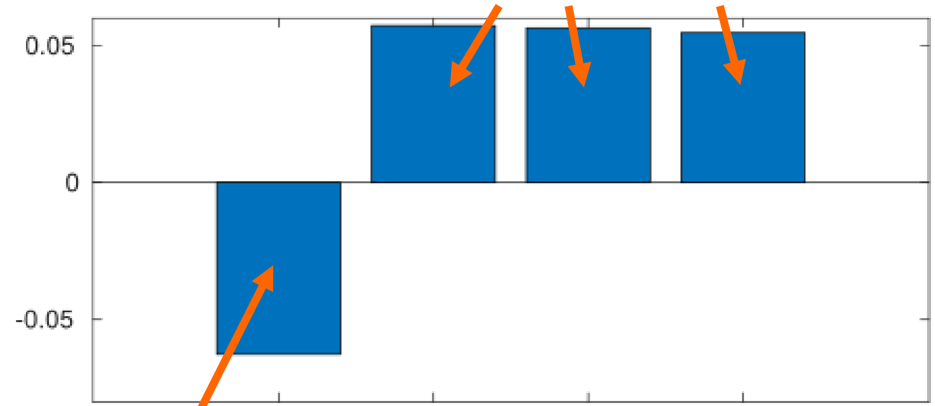
Provincial vs connector hub
Accuracy:
Training 53.23%
Test 52.57%
(> Random 50.38%)

φ_{spat} predicts hubness



Hubs have lower internal density, high φ_{st}, and uniform in-ROI correlations

φ_{spat}, varying correlations, and φ_{st} predict provincial role

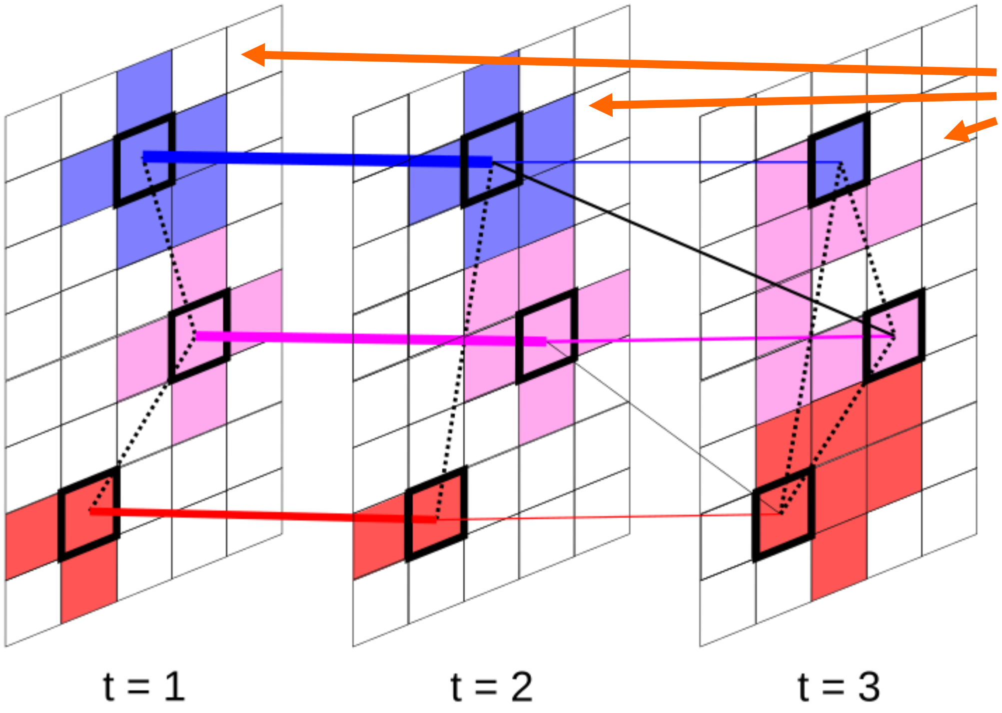


Low internal density = connector hub

Possible solution: time-dependent nodes

(ongoing, 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

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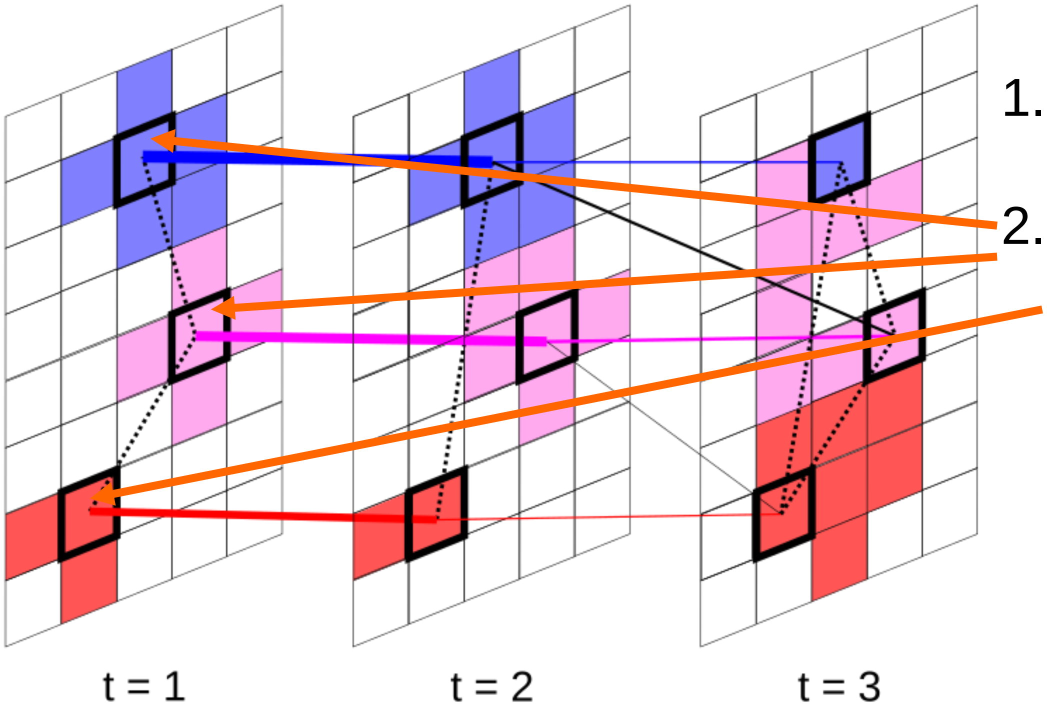

1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)

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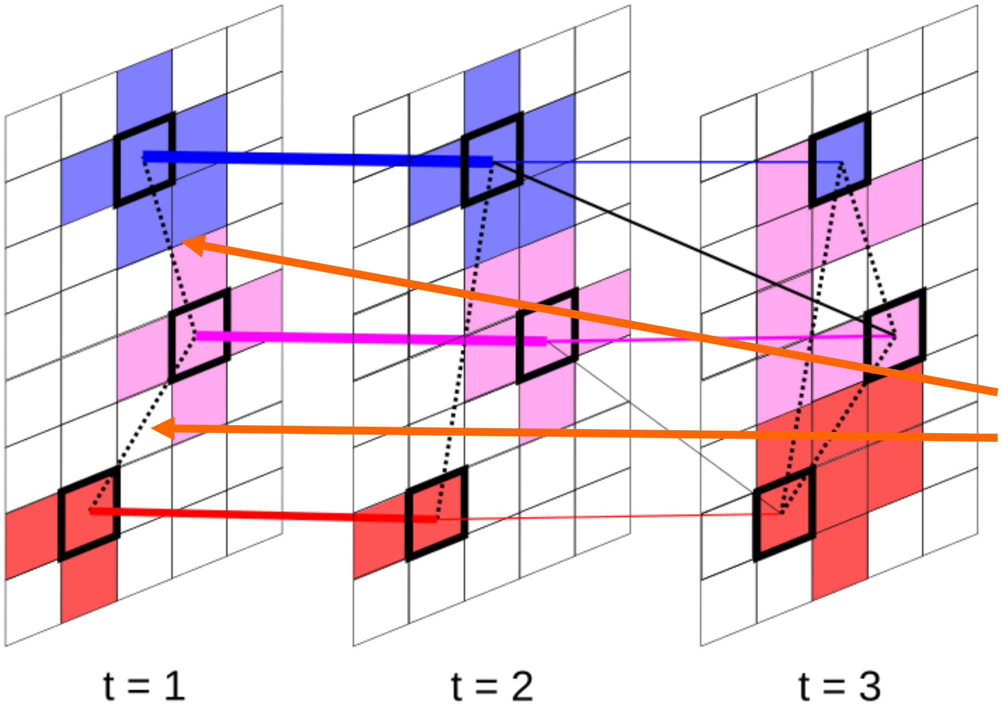

1. Layers = time windows
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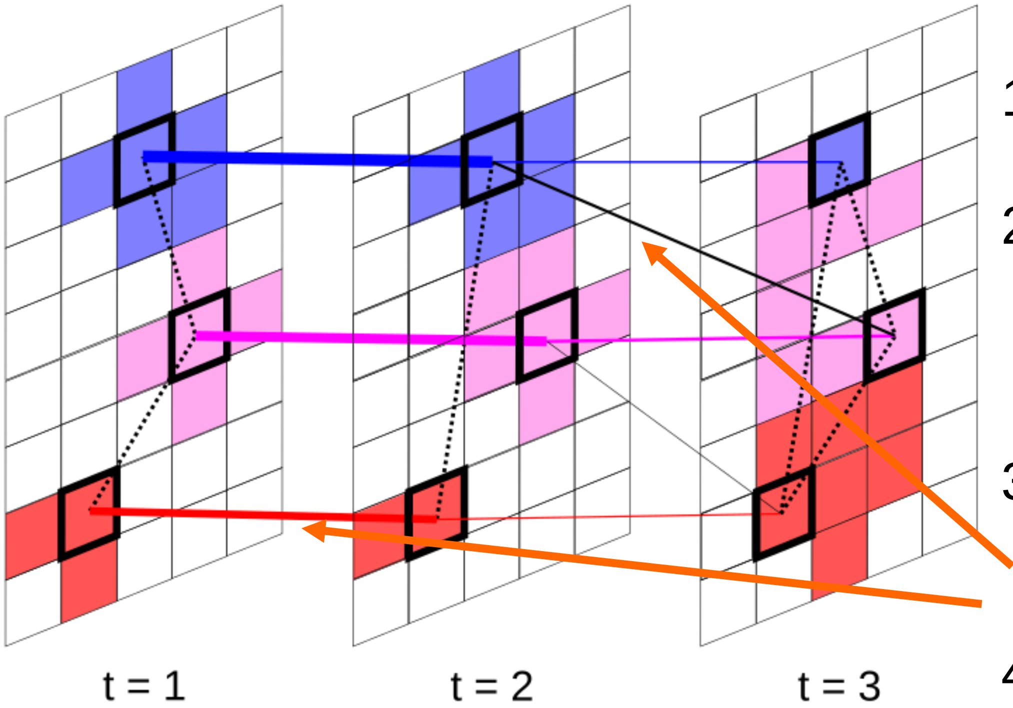

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4. Interlayer links = spatial overlap

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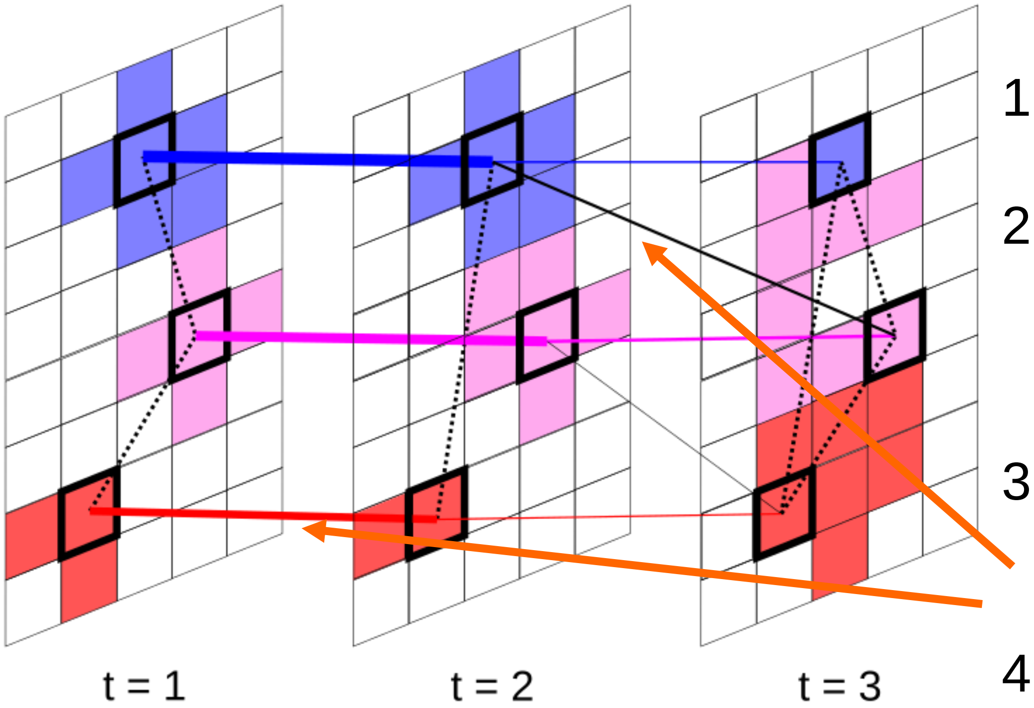

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2. ROIs optimized inside layers for maximal homogeneity (voxel-level clustering)
3. Intralayer links = Pearson correlation
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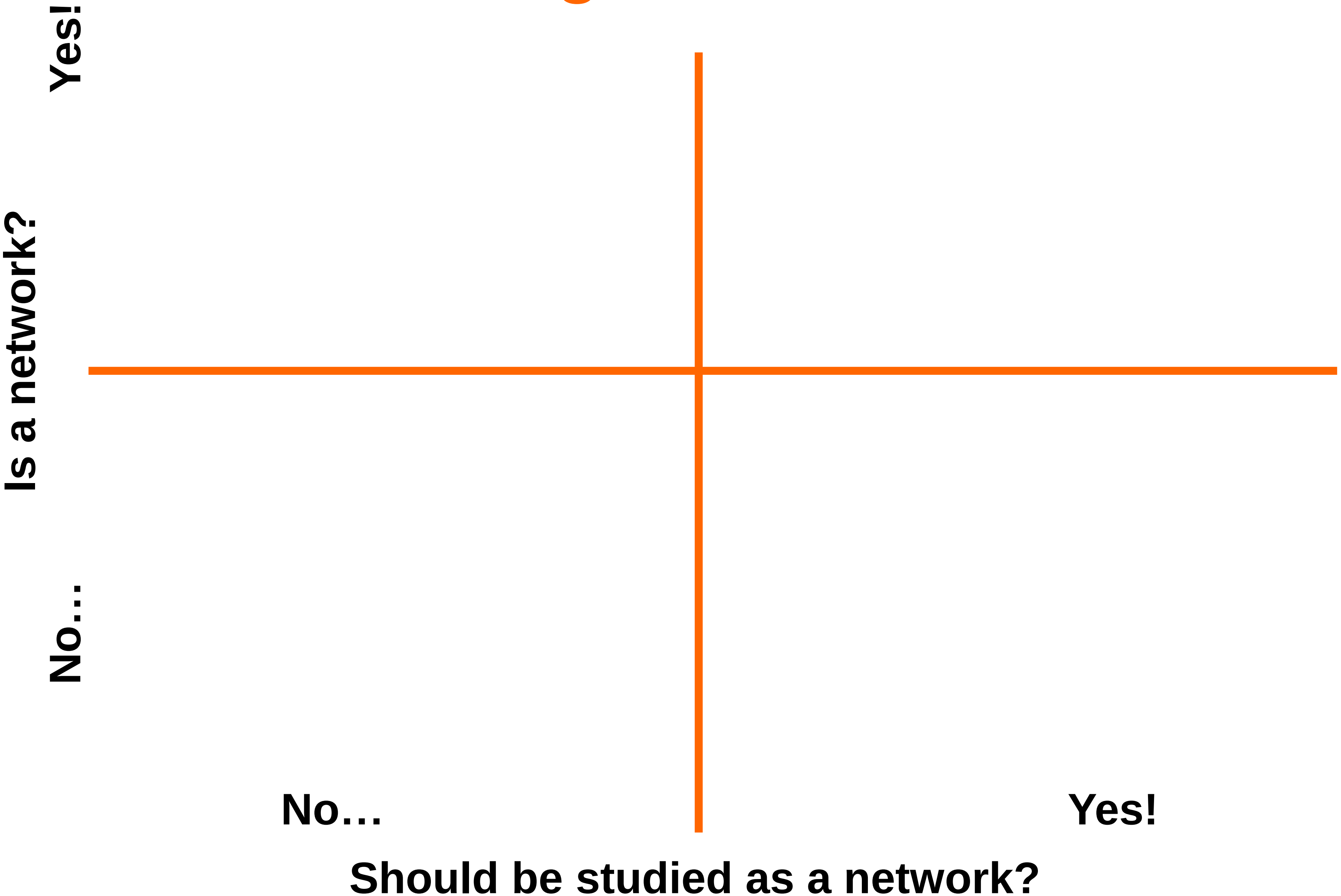
Questions:

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

Not all that glitters is a network



Yes!

Is a network?

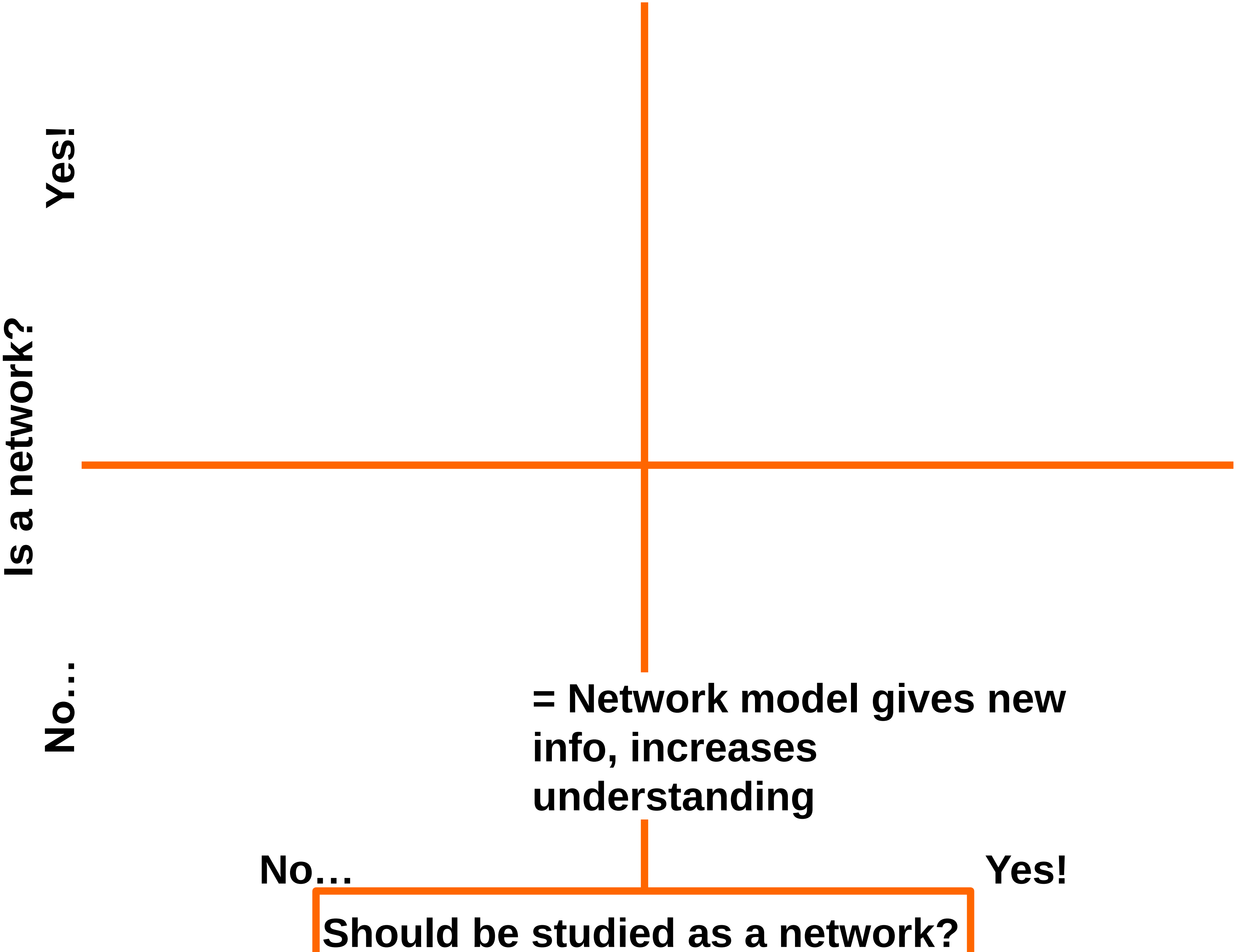
No…

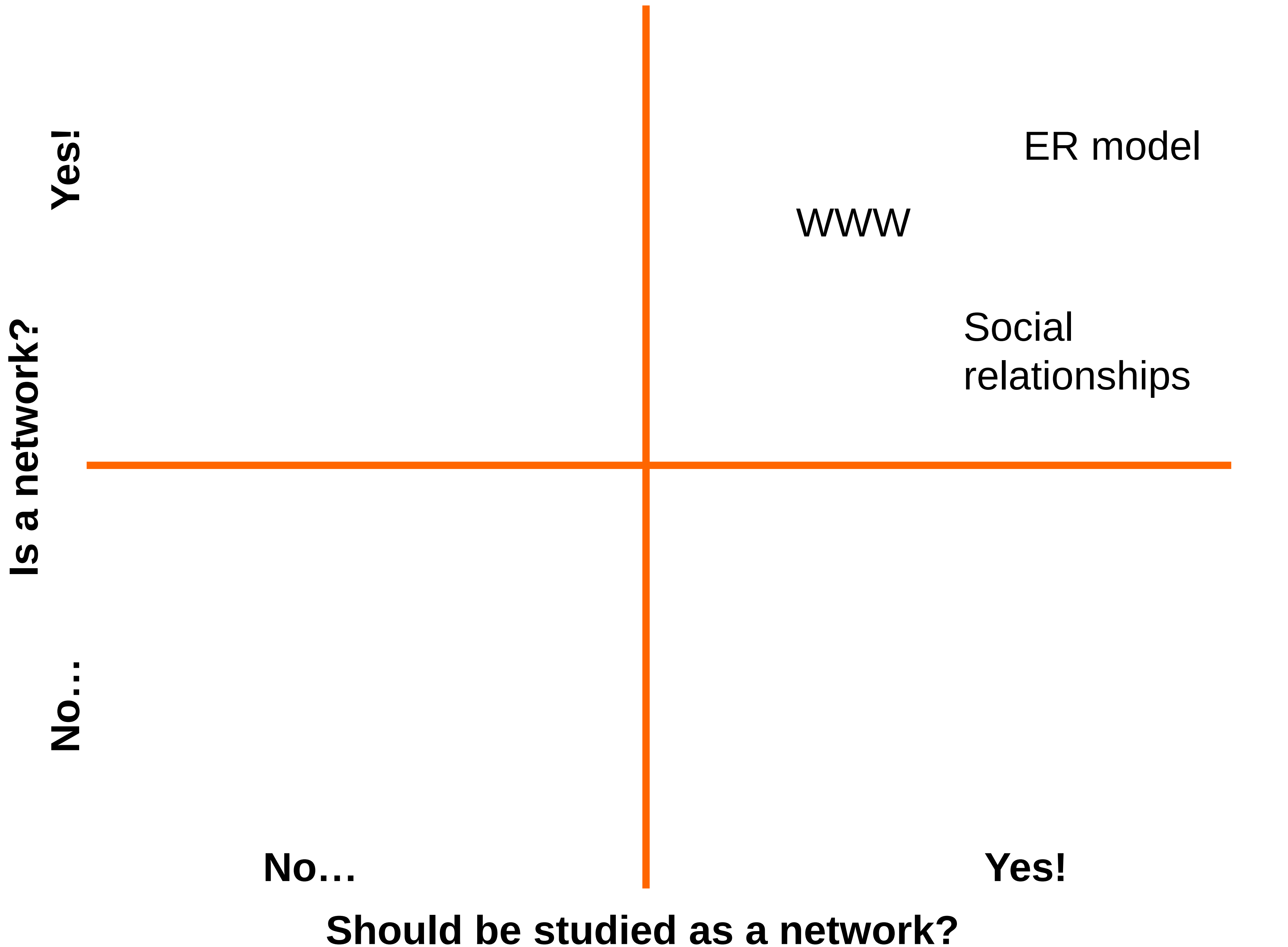
= Essentially consists of nodes and links

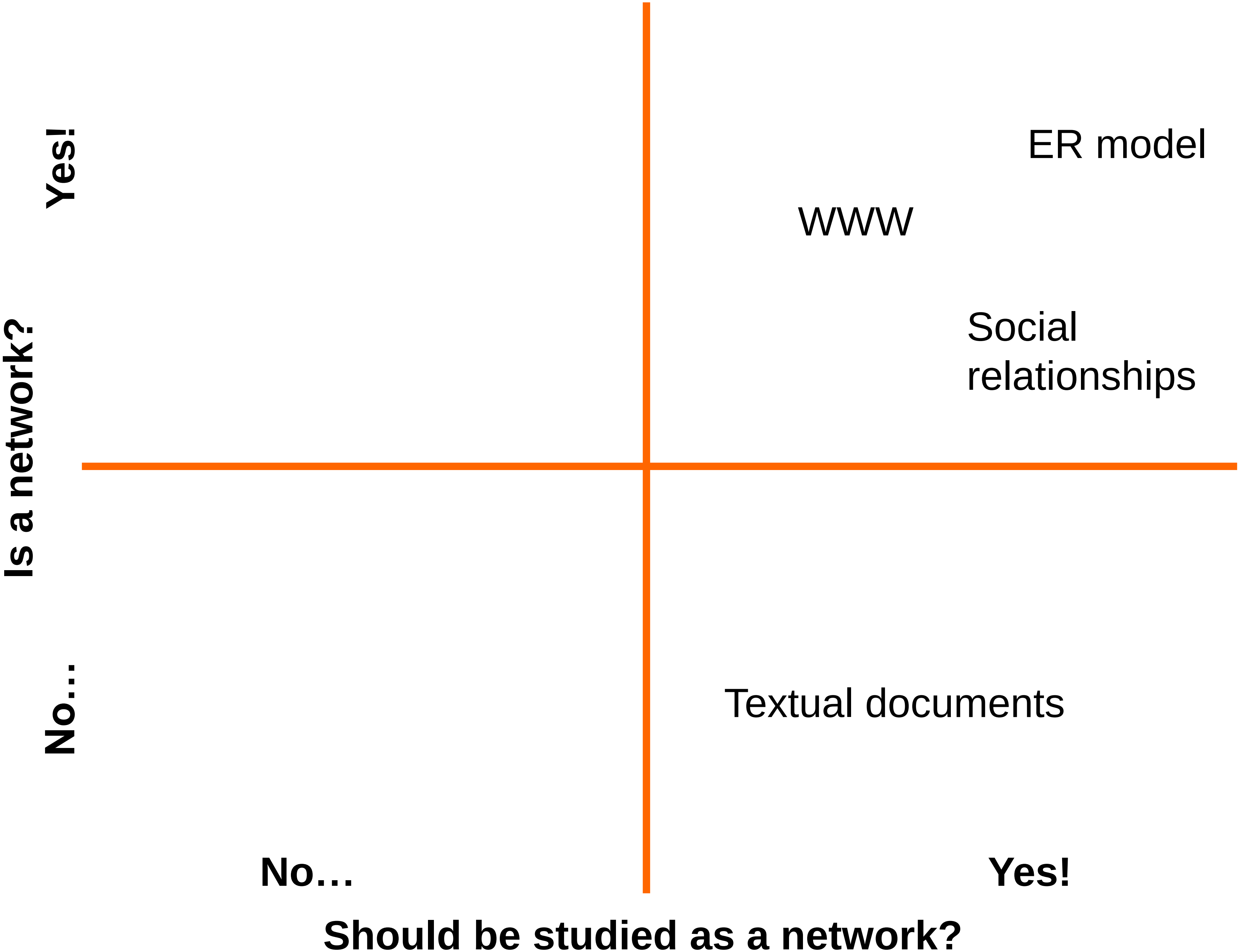
Has tangible nodes and links (J. Saramäki)

No… Yes!

Should be studied as 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?
Yes!
No…
ER model
WWW
Social relationships
No…
Yes!
Should be studied as a network?



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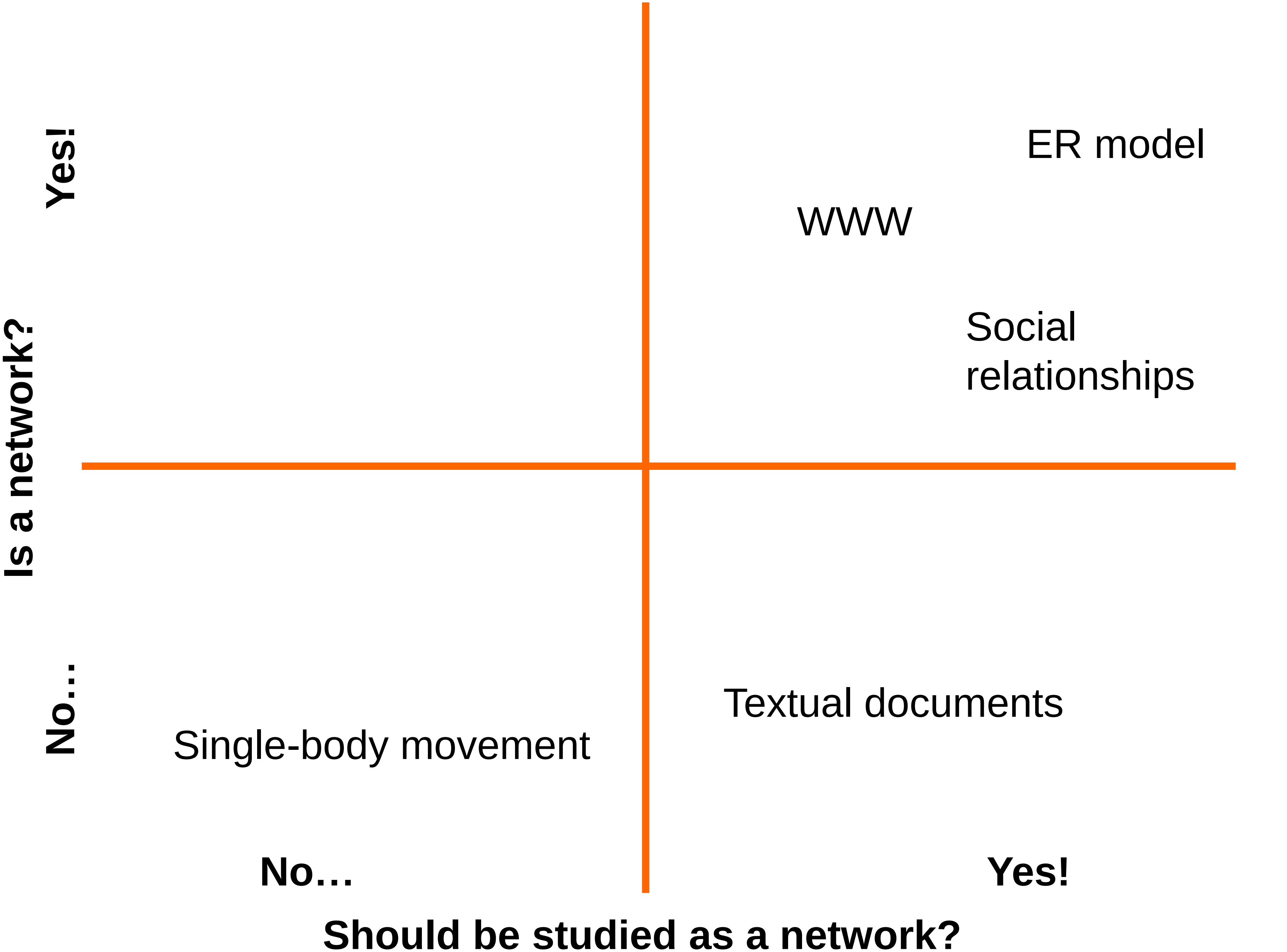
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Single-body movement
No…
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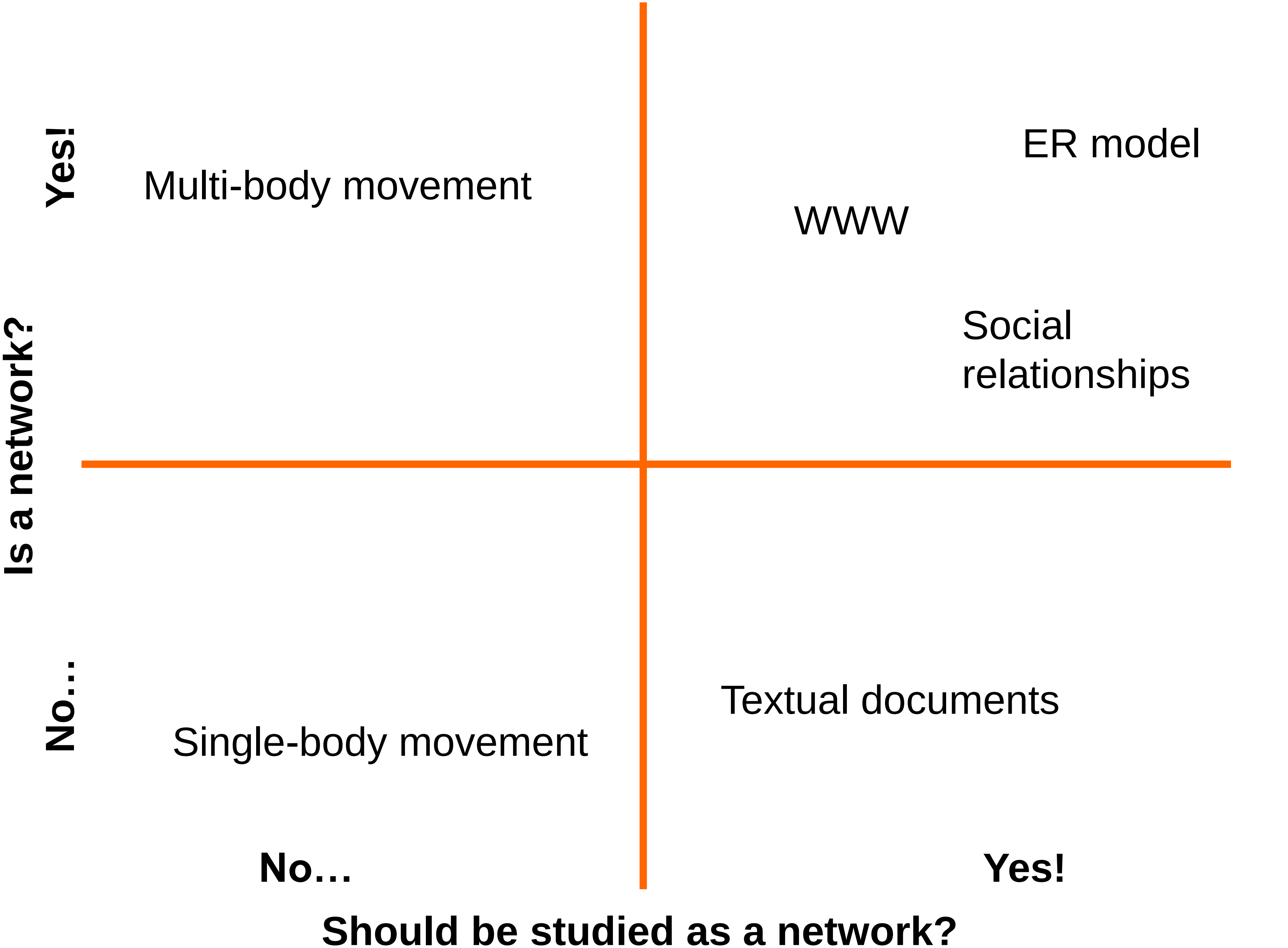
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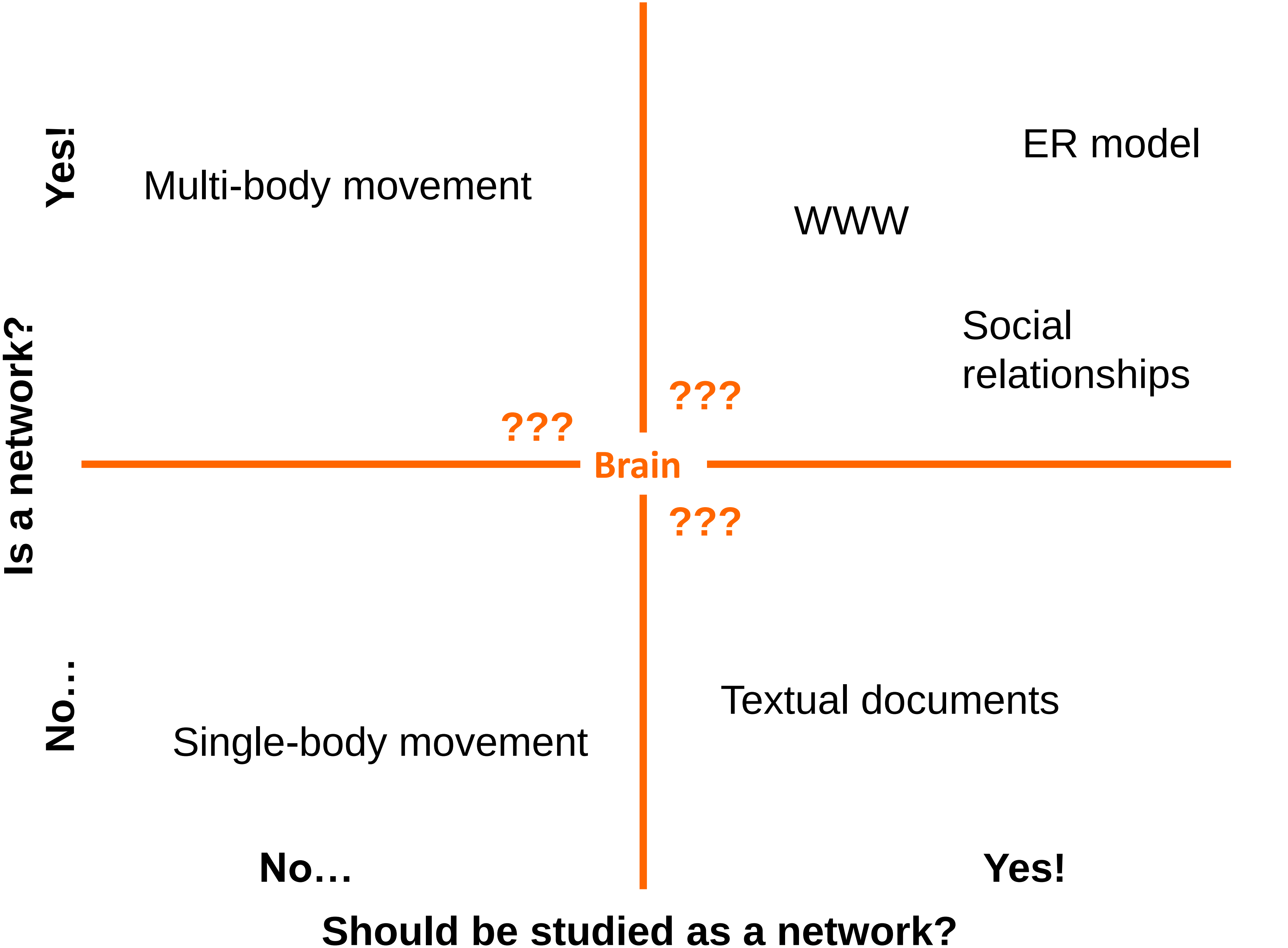
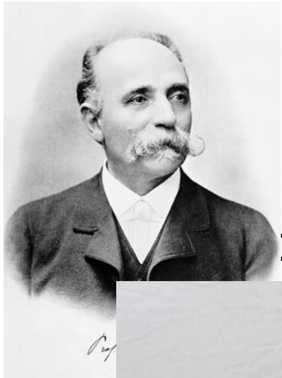

ER model
Yes!
Multi-body movement
WWW
Social relationships
Is a network?
???
???
Brain
???
No…
Textual documents
Single-body movement
No…
Yes!
Should be studied as a network?

Figs: Wikimedia Commons, public domain



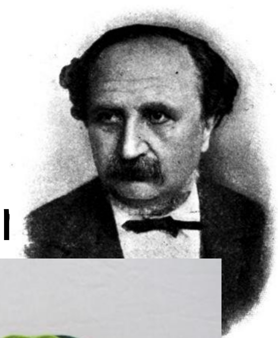


Photo: Milja Heikkinen

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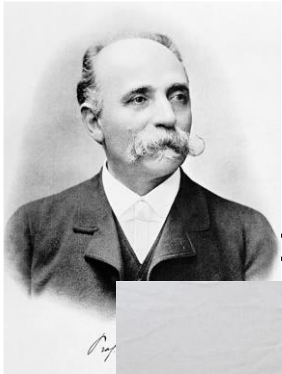

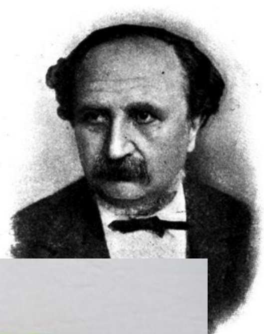

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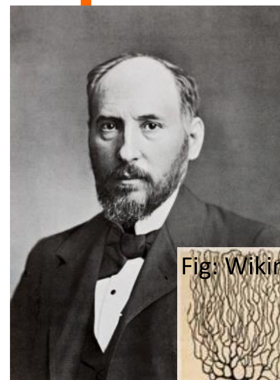
Photo: Milja Heikkinen

Fig: Wikimedia Commons, public domain



ER model

WWW

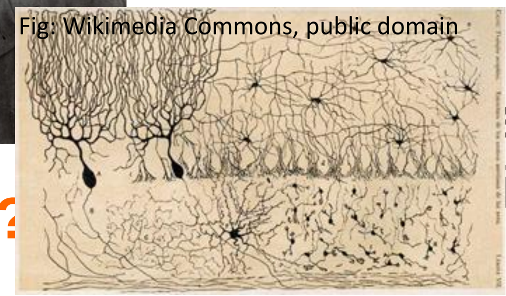


Fig: Wikimedia Commons, public domain

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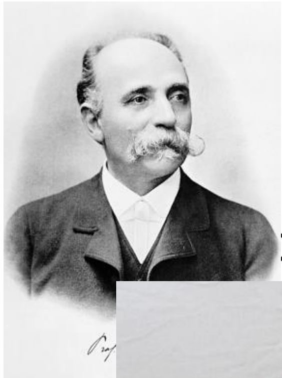
Figs: Wikimedia Commons, public domain



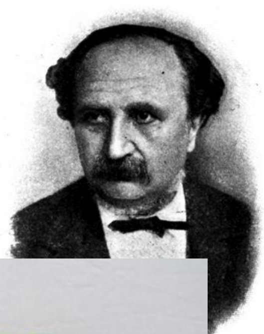


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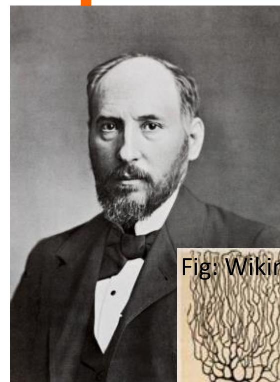
Photo: Milja Heikkinen

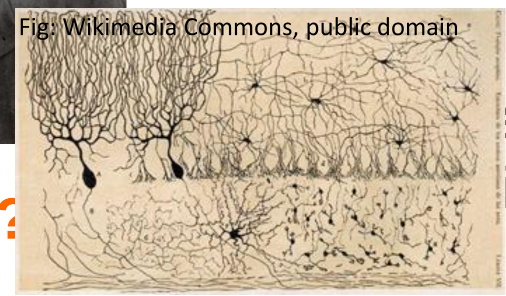
Fig: Wikimedia Commons, public domain



ER model

WWW

Fig: Wikimedia Commons, public domain



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Yes!

Is a network?

Brain

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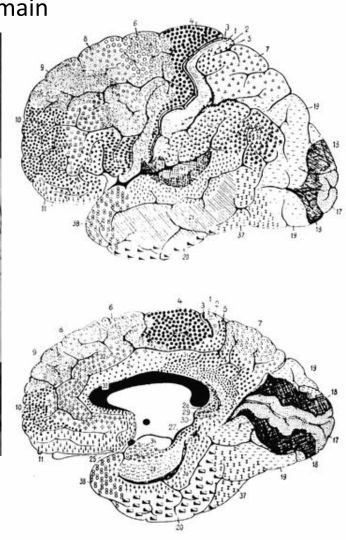
Figs: Wikimedia Commons, public domain



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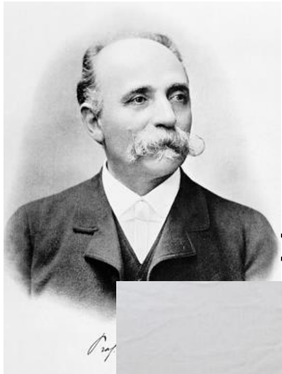
Textual documents

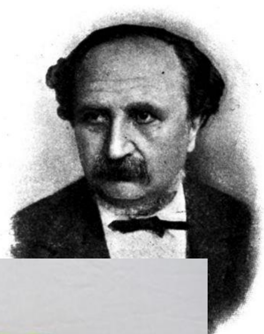
No..

Yes!

Should be studied as a network?

Figs: Wikimedia Commons, public domain





Yes!

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Photo: Milja Heikkinen

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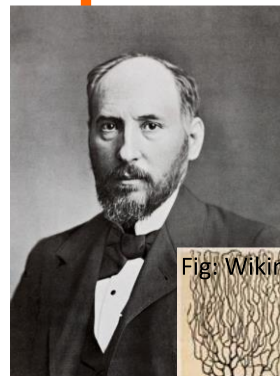

ER model

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Fig: Wikimedia Commons, public domain

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White et al. 1968: *C. elegans*

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Is a network?

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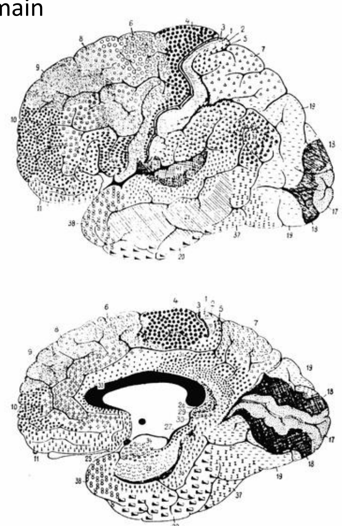

Textual documents

No..

Yes!

Should be studied as a network?

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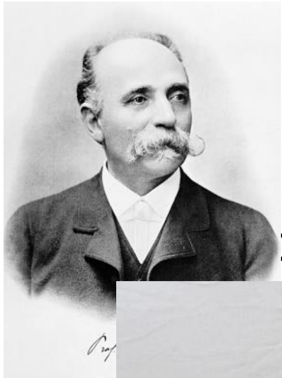

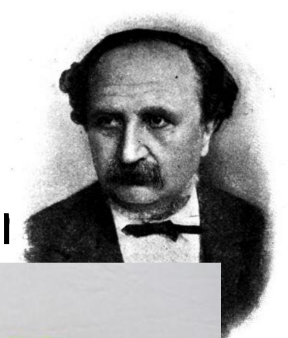

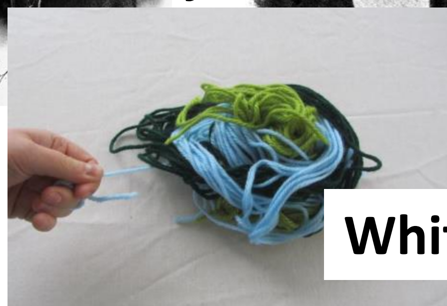

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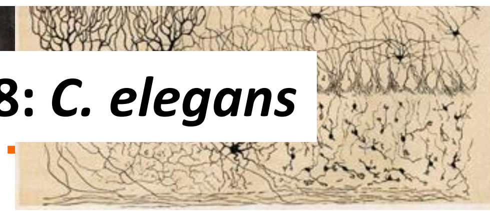
Bassett & Muldoon 2016, Bassett & Sporns 2017: network neuroscience

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



White et al. 1968: *C. elegans*

Yes!

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Brain

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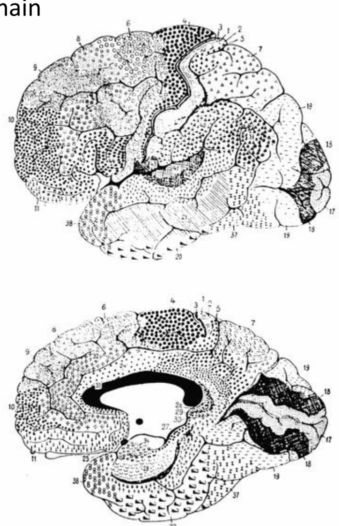


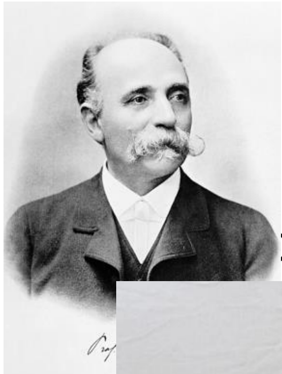
Textual documents

Is a network?

No.. **Yes!**

Should be studied as a network?

Figs: Wikimedia Commons, public domain



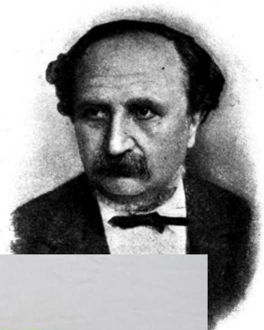


Fig: Wikimedia Commons, public domain

Yes!

Is a network?

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

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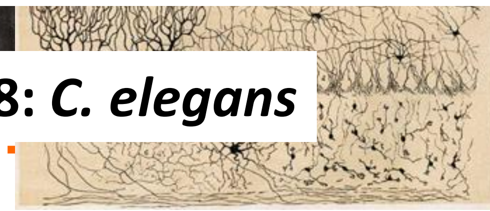

White et al. 1968: *C. elegans*

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Brain

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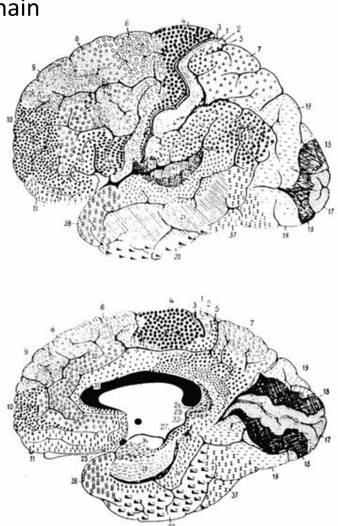

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how to define nodes/links?

structure/function?

correlation = causation?

No..

Yes!

Should be studied as a network?

Conclusions

- Network neuroscience = studying the brain with network tools
- Constructing functional brain networks is not trivial
  - Node definition?
  - Preprocessing, space, thresholding, link definition, interpretation of analysis outcomes?
  - **Know your methods (and questions)!**
- Currently used nodes functionally inhomogeneous
  - Effects on observed connectivity?
  - Homogeneity changes in time (+ related to function)
  - Flexible nodes a possible solution
- Not everything that glitters is a network – is the brain?
  - **Critical thinking and discussion needed!**

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Thank you!

Questions, comments?

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Slides: https://github.com/onerva-korhonen/presentations/blob/master/ifisc_261022.pdf