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School of Science

Brain networks
Current state and future challenges

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PART 1
Brain networks
ABC

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The Brain according to wikipedia

…The brain is the most **complex** organ in a vertebrate's body…

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The Brain according to wikipedia

…In a typical human the **cerebral cortex** (the largest part) is estimated to contain

15–33 billion (**10^9!!**) neurons

each **connected** by synapses to **several thousand** other neurons…

Why do we want to study brain networks?

- **The brain is a network with**
  ~10^10 neurons and ~10^4 connections per neuron
- As for **genomics** in the 20th century, many authors are now praising the ***connectomics*** as the current revolution in neuroscience
- Multi-million projects like the **Human *Connectome* Project, the BRAIN initiative**
- **Charting the *connectome*** presents challenges

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What is a connectome?

The connectome

The connectome is the complete description of the structural connectivity (the physical wiring) of an organism's nervous system.

Olaf Sporns (2010), Scholarpedia, 5(2):5584.

Structure and Function

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Many types of networks

- Physical networks
  - *Power grid network*
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- Non-physical networks
  - *Social networks (Facebook, Twitter, etc.)*
  - *Stock Market*
  - *IP layer of the internet*

Brain networks

- **Structural connectivity (estimating actual connections, the connectome)**
- **Functional connectivity (based on temporal "co-variance")**

Craddock, et al. (2013). Imaging human connectomes at the macroscale. Nature Methods, 10(6), 524–539. (*)


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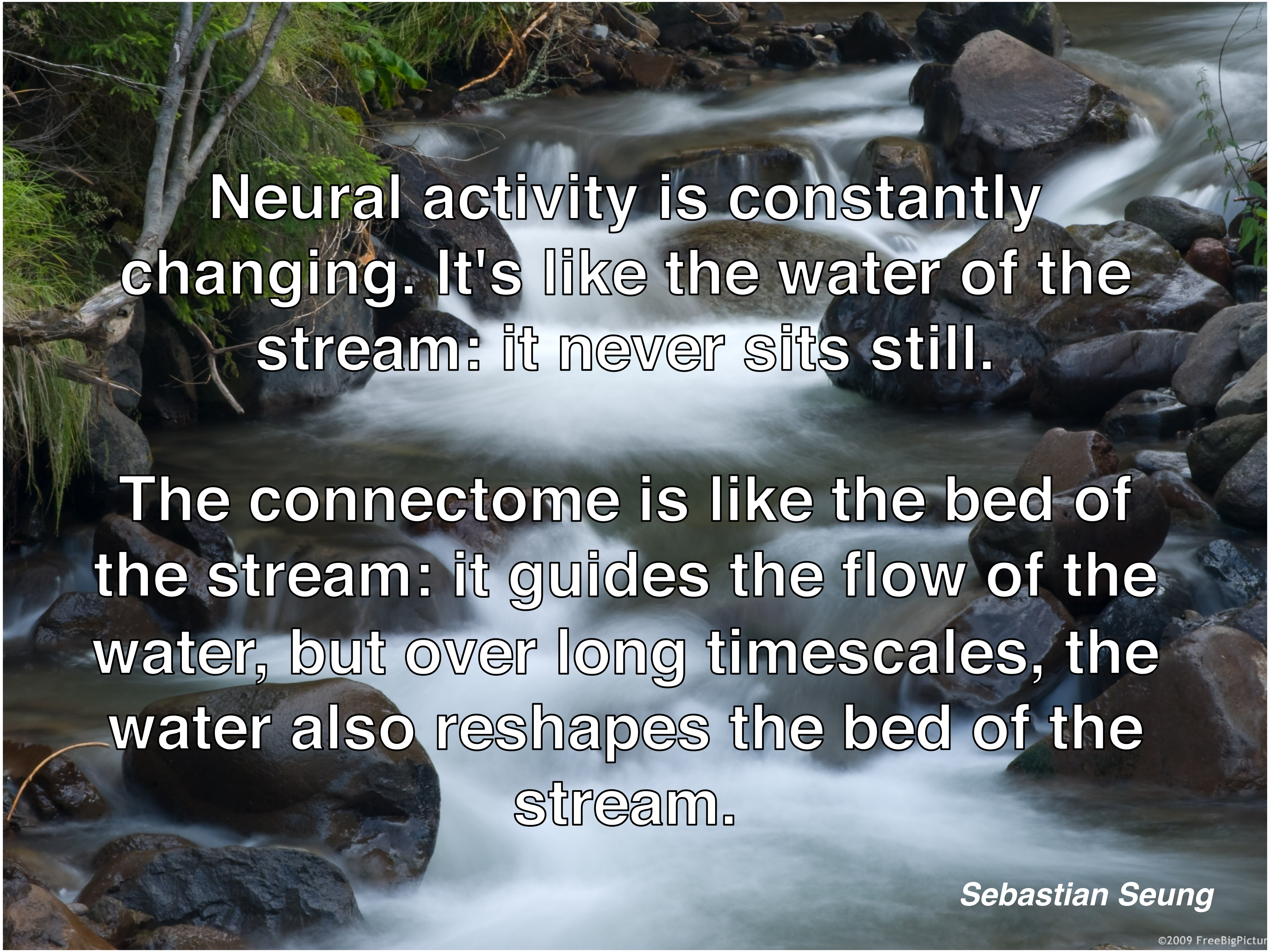
Neural activity is constantly changing. It's like the water of the stream: it never sits still.
The connectome is like the bed of the stream: it guides the flow of the water, but over long timescales, the water also reshapes the bed of the stream.
Sebastian Seung
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Connectivity in neuroscience

- **Structural connectivity (estimating actual connections)**
  - ***Invasive*** *(tract tracing methods, 2 photon calcium imaging)*
  - ***Non invasive*** *(Diffusion Tensor and Diffusion Spectral Imaging)*
- **Functional connectivity (based on temporal "co-variance")**
  - ***Invasive*** *(intracranial recordings)*
  - ***Non invasive*** *(fMRI, M/EEG, simulated data)*

Craddock, et al. (2013). Imaging human connectomes at the macroscale. Nature Methods, 10(6), 524–539. (*)

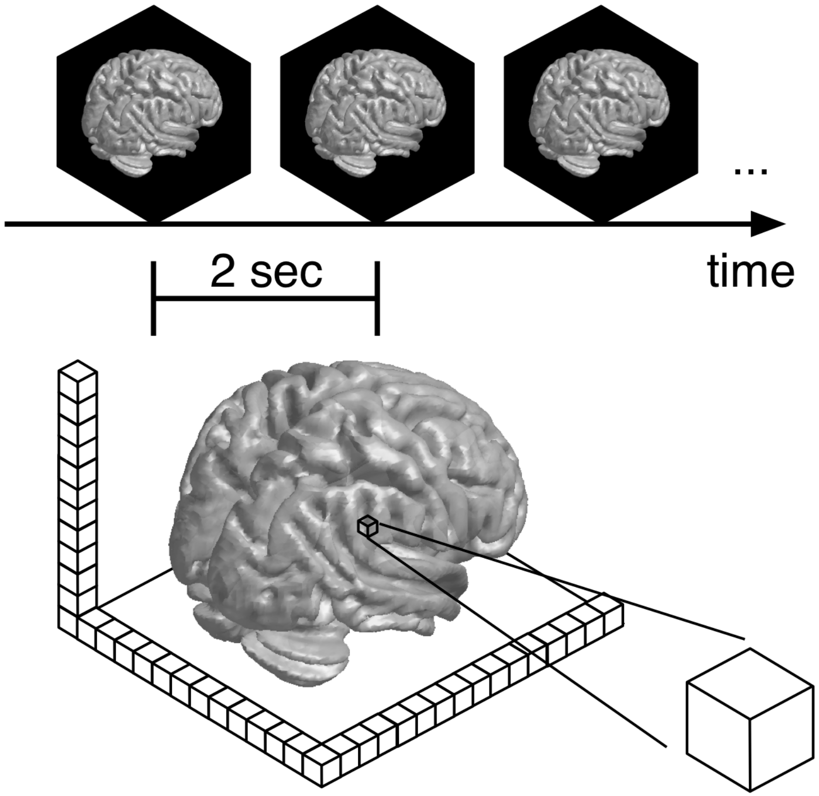
Brain networks – general principles

- **Geographical networks:** nodes are located in 3D space and each node has specific function
- **Hierarchically structured**: with highly reproducible modules both at structural and functional level
  - *Possibly arising from* ***wiring economy*** *Rivera-Alba, M.et al (2014). Wiring economy can account for cell body placement across species and brain areas. Current Biology, 24(3), R109-R110.*
- **Multiple instances:**
  - *we can estimate brain networks from* ***multiple subjects*** *or from the same subject at* ***multiple time points***
  - *we can estimate brain networks from same subject using* ***multiple techniques***
- **Computing network-level statistics (p values!):**
  - *what is significantly similar across subjects/time-points/techniques*
  - *What is significantly different (e.g. between groups or conditions)*

Connectomes, spatial scales and imaging techniques

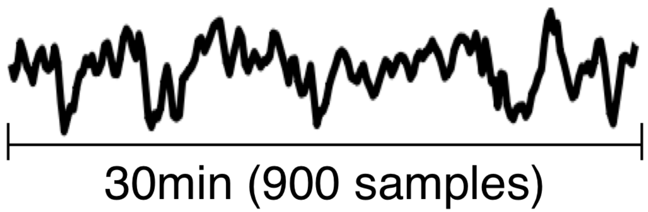
- **Microscopic scale** (i.e. actual neurons): worm, fruit fly, mouse retina [electron microscope or 2 photon imaging]
- **Mesoscopic scale** (based on neuronal tracing): mouse, macaque [usually viral neuronal tracing antero/retrograde transport -> one connection per animal]
- **Mesoscopic/macroscopic scale** (structural non invasive) [MRI, PET, DTI/DSI]
- **Mesoscopic/macroscopic scale** (functional non invasive) [fMRI, M/EEG]

Functional magnetic resonance imaging (fMRI)



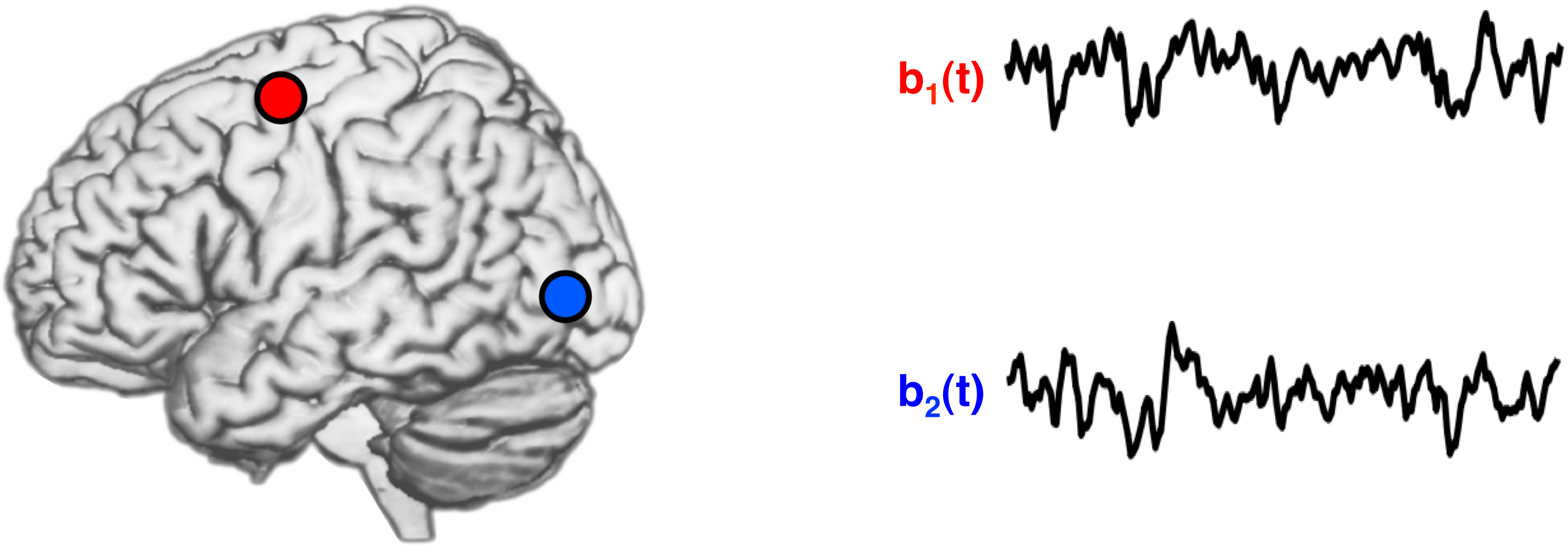
- We measure **multiple time series** at once
- **NOTE:** 1 voxel -> 5.5e6 neurons 4e10 synapses (density ~1/1000) [Logothetis 2008 Nature]

Blood Oxygen Level signal



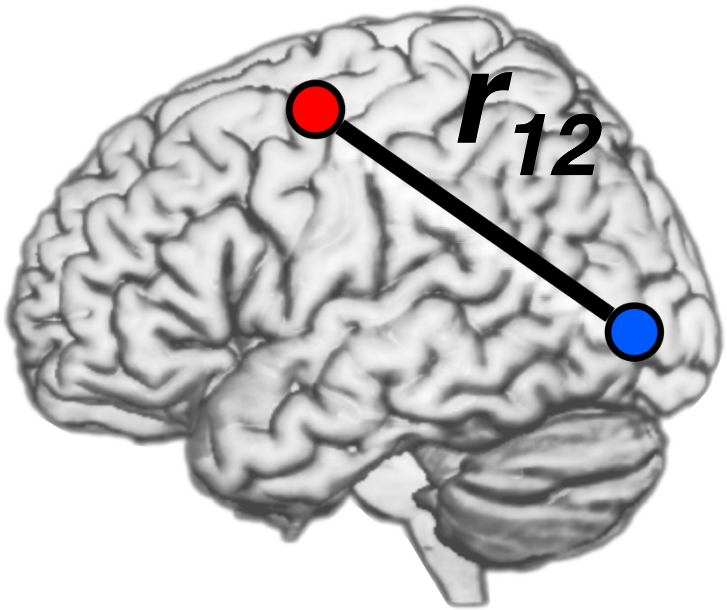
Building a functional network

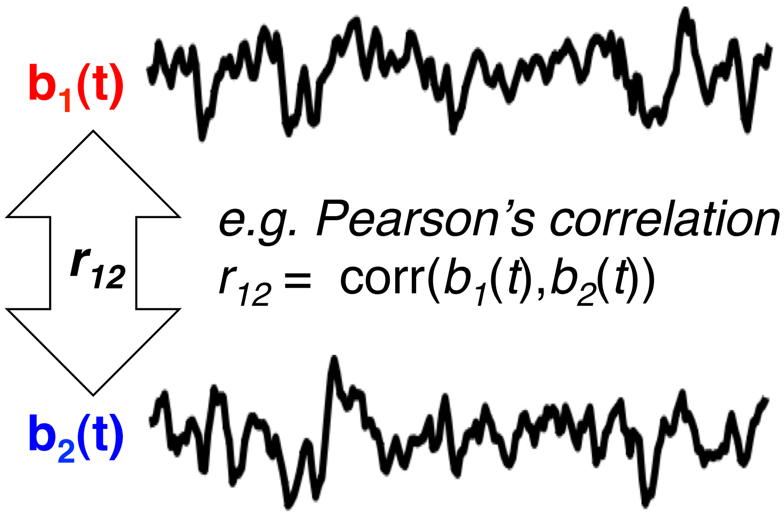
At each **node** we measure a **time series**
We compute their **similarity**



Building a functional network

Similarity value used as **weight of the edge** between the two nodes. Repeat for each pair of nodes.





e.g. Pearson's correlation:
$r_{12} = \text{corr}(b_1(t), b_2(t))$

PART 2
Brain networks
Current state

Brain networks in animals

Why is it important?

- It’s our only chance to estimate **actual connectomes**
- Only way to scale models from **micro/neuronal to macro/functional** and possibly the other way around
- Fascinating painstaking work of labelling each neuron and its synaptic contacts to **understand brain circuits**
- Videos from TED Talk “I am my Connectome”

Brain networks in animals
Known connectomes so far

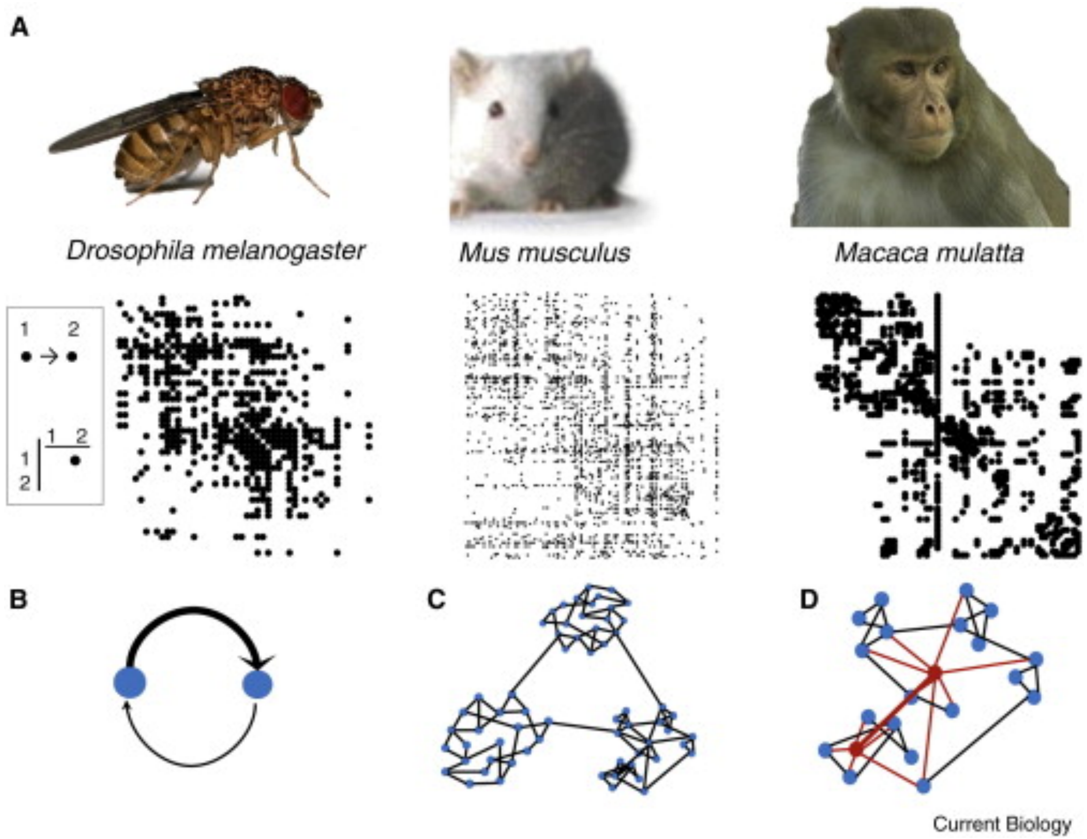
	C. elegans hermaphrodite (or male)	*Fruit fly medulla column(s)*	*Mouse retina IPL segment*	*Fruit fly brain*	*Mouse cortical column*	*Mouse brain*	*Human brain*
Volume in mm^3	*0.0003*	*0.0001*	*0.001*	*0.071*	*0.12*	*450*	*1,400,000*
Voxel dimensions X×Y×Z,nm	*5×5×70*	*3.1×3.1×40*	*16×16×25*	*$\sim 8^3$*	*$\sim 15^3$*	*$\sim 15^3$*	*$\sim 15^3$*
Voxel volume, nm^3	*~1750*	*380*	*6800*	*~500*	*~3400*	*~3400*	*~3400*
Voxels, $x10^{12}$	*0.13*	*0.3*	*0.15*	*142*	*35*	*130K*	*280M*
Neurons traced	*302*	*379*	*950*	*$\sim 10^5$*	*$\sim 10^4$*	*$\sim 10^8$*	*$\sim 10^{11}$*
Synapses annotated	*7283*	*8637*	*-*	*$\sim 10^8$*	*$\sim 10^8$*	*$\sim 10^{12}$*	*$\sim 10^{15}$*
Proof time (person-year)	*>10*	*10*	*10*	*4700*	*1200*	*4.5M*	*14G*

Plaza, S. M., Scheffer, L. K., & Chklovskii, D. B. (2014). Toward large-scale connectome reconstructions. Current opinion in neurobiology, 25, 201-210.

Brain networks in animals & network science – Resources

- All connectomes known so far stored in **multiple online databases**
  - *Open Connectome* *http://openconnecto.me/graph-services/download/*
  - *Allen Institute Brain Atlases* *http://connectivity.brain-map.org/*
  - *NIH Blueprint non-human primate atlas* *http://www.blueprintnhpatlas.org/*
- Oh, S. W., Harris, J. A., Ng, L., Winslow, B., Cain, N., Mihalas, S., ... & Mortrud, M. T. (2014). A mesoscale connectome of the mouse brain. Nature, 508(7495), 207-214.
- Shih, C. T., Sporns, O., Yuan, S. L., Su, T. S., Lin, Y. J., Chuang, C. C., ... & Chiang, A. S. (2015). Connectomics-based analysis of information flow in the Drosophila brain. Current Biology, 25(10), 1249-1258.
- Rubinov, M., Ypma, R. J., Watson, C., & Bullmore, E. T. (2015). Wiring cost and topological participation of the mouse brain connectome. Proceedings of the National Academy of Sciences, 112(32), 10032-10037.

Brain networks across species/scales (universality?)



Kaiser, M. (2015). Neuroanatomy: Connectome Connects Fly and Mammalian Brain Networks. Current Biology, 25(10), R416-R418.

- Goulas, A., et al. (2014). Comparative analysis of the macroscale structural connectivity in the macaque and human brain. PLoS Comput Biol, 10(3), e1003529.

- van den Heuvel, MP, et al. (2015). Bridging cytoarchitectonics and connectomics in human cerebral cortex. The Journal of Neuroscience, 35(41), 13943-13948.

From animals to humans

Connectivity in neuroscience… non invasively

- **Structural connectivity (estimating actual connections)**
  - ***Invasive*** *(tract tracing methods, 2 photon calcium imaging)*
  - ***Non invasive*** *(Diffusion Tensor and Diffusion Spectral Imaging)*
- **Functional connectivity (based on temporal "co-variance")**
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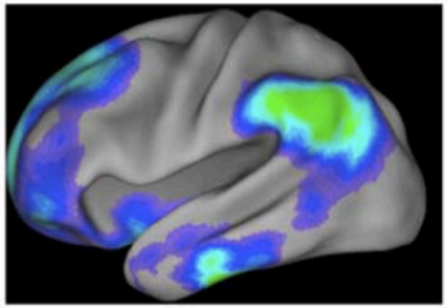
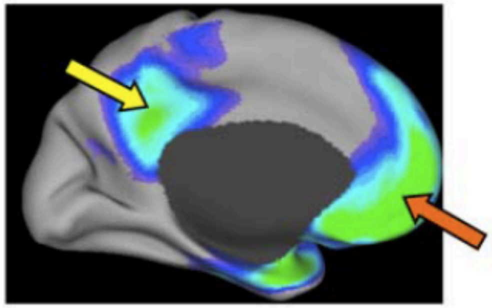
Craddock, et al. (2013). Imaging human connectomes at the macroscale. Nature Methods, 10(6), 524–539. (*)

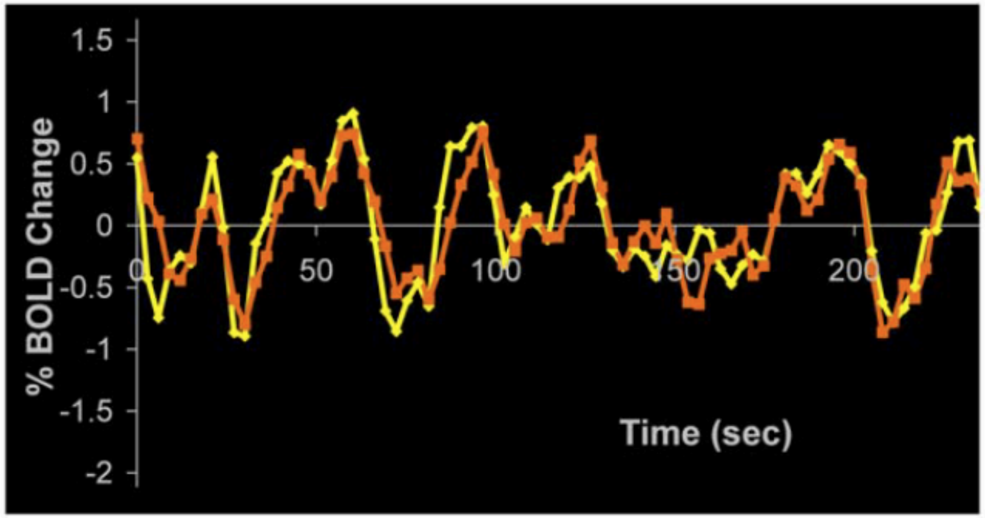
The brain at rest

The activity of the brain at rest is ideal for estimating the connectome

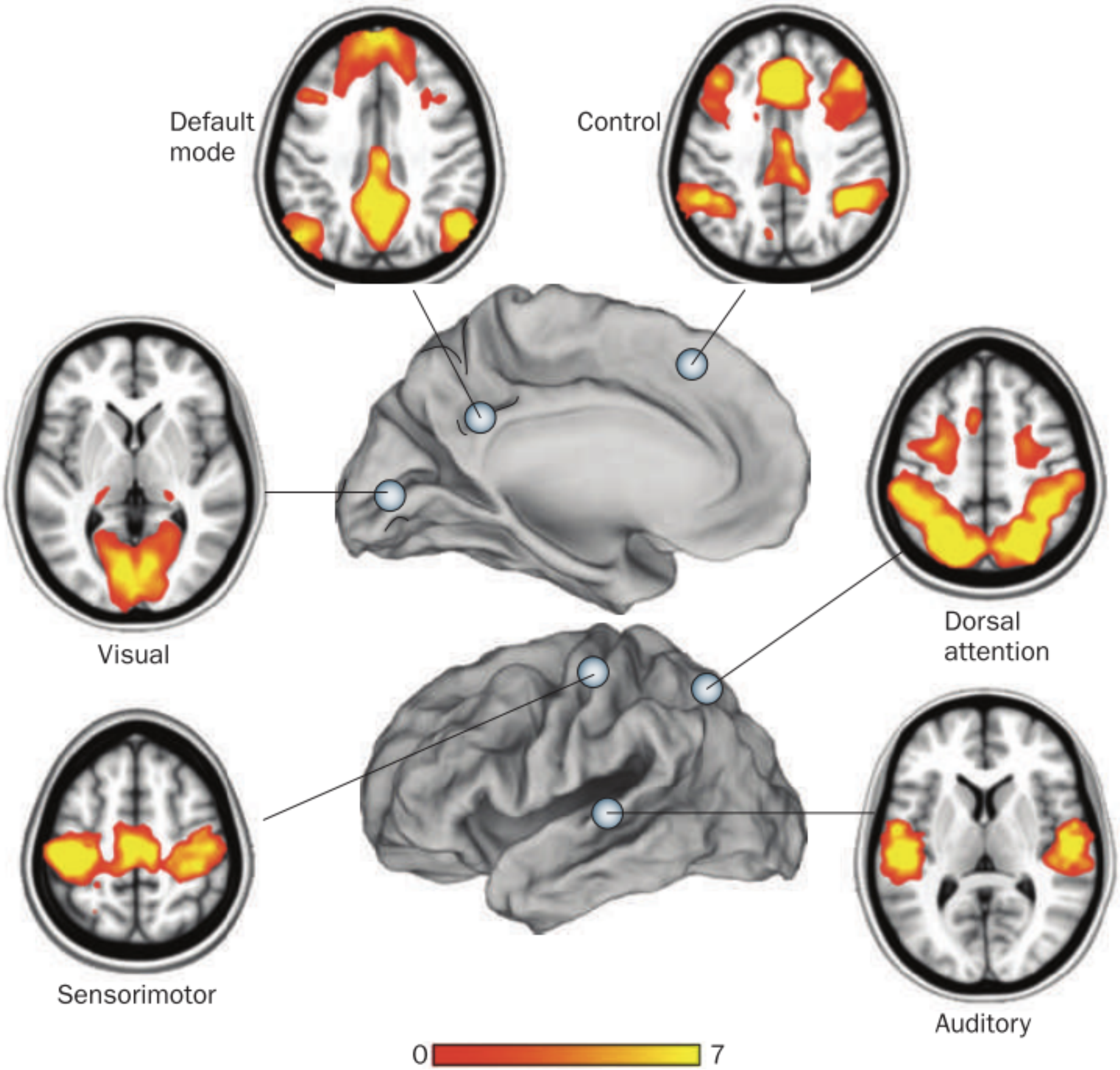
By looking at regions that change together in time we can **estimate their connectivity**



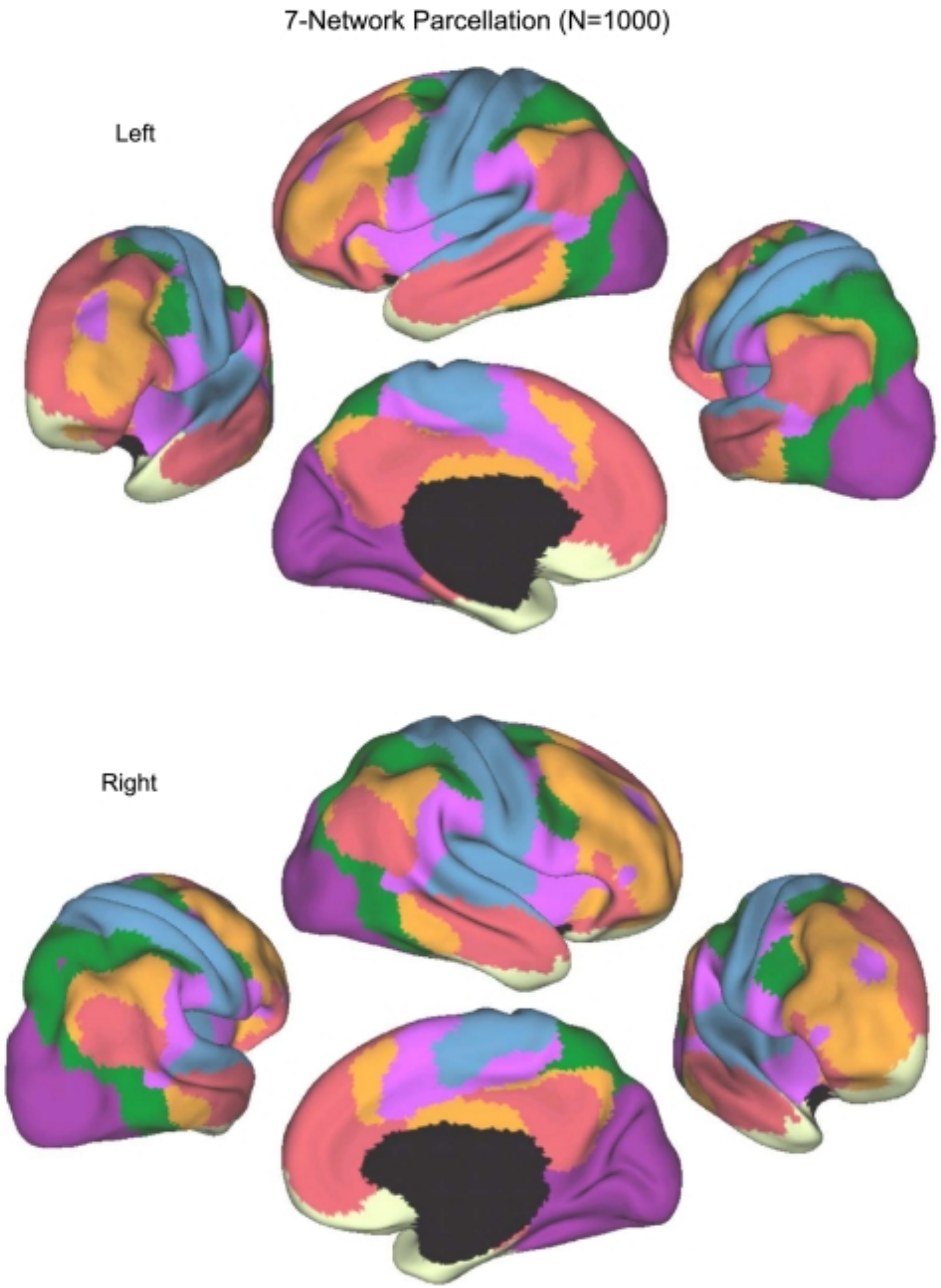




Raichle, M. E. (2010). Two views of brain function. Trends in Cognitive Sciences, 14(4)



Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. Nature reviews. Neurology, 6(1), 15–28.



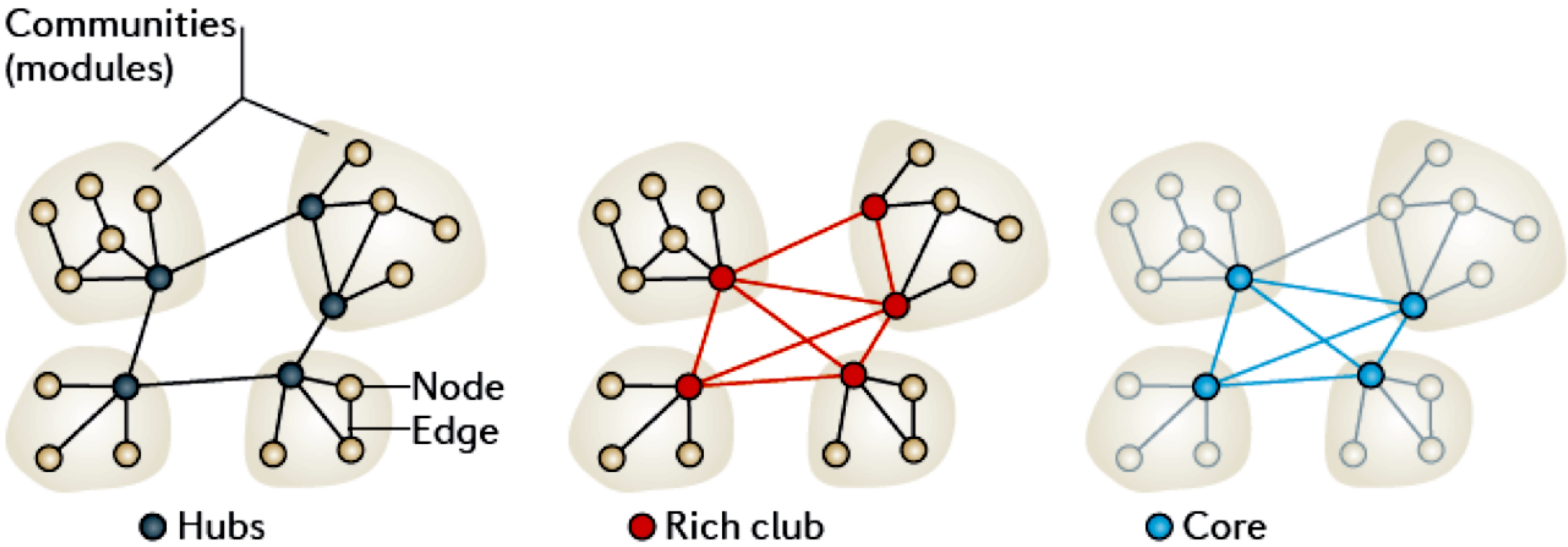
- Purple (Visual)
- Blue (Somatomotor)
- Green (Dorsal Attention)
- Violet (Ventral Attention)
- Cream (Limbic)
- Orange (Frontoparietal)
- Red (Default)

Yeo et al. (2011)

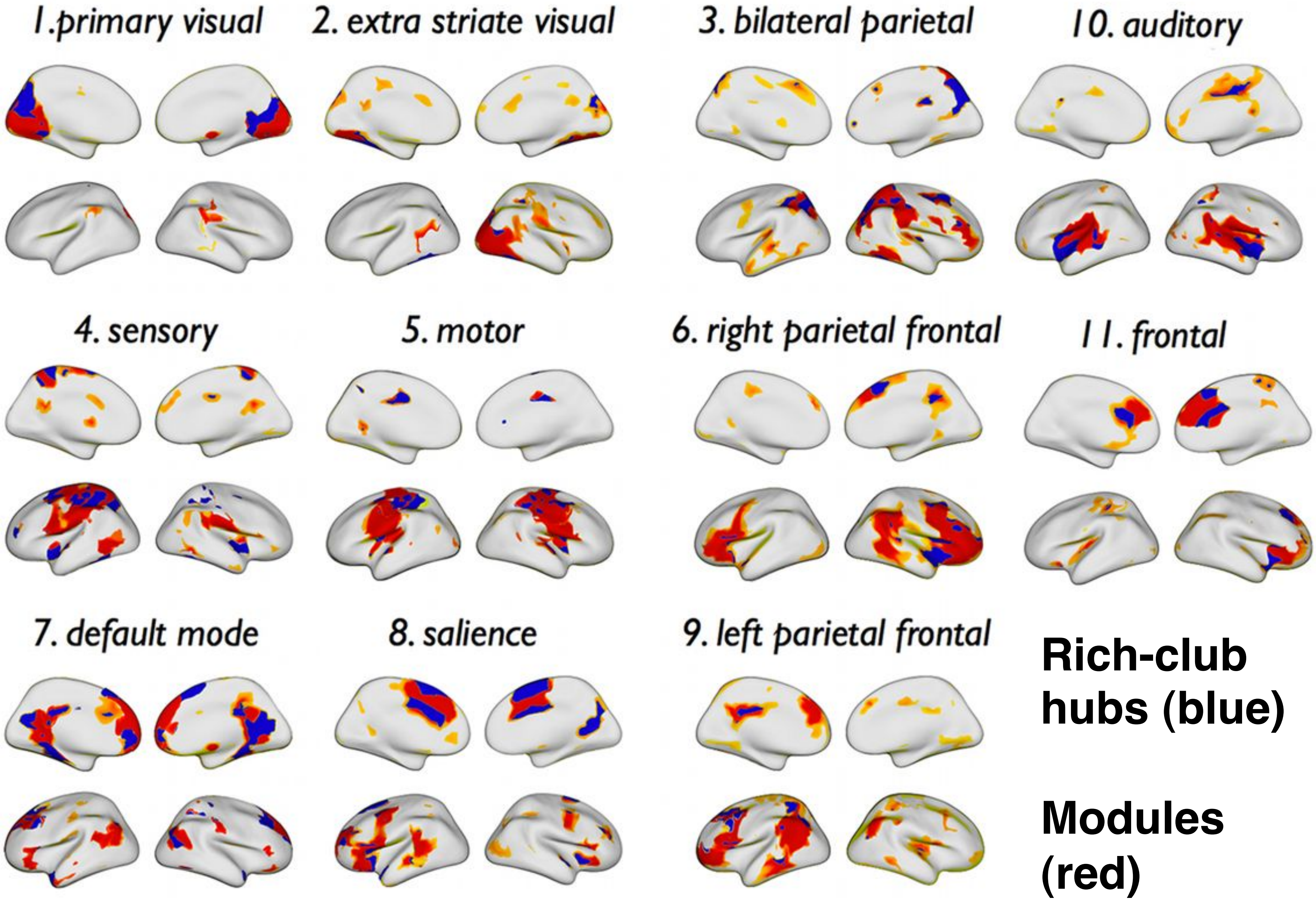
The organization of the human cerebral cortex estimated by intrinsic functional connectivity

J Neurophysiol. 106(3):1125-65.

A *rich club* of strong hubs in multiple modules is at the core of the human brain



Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49



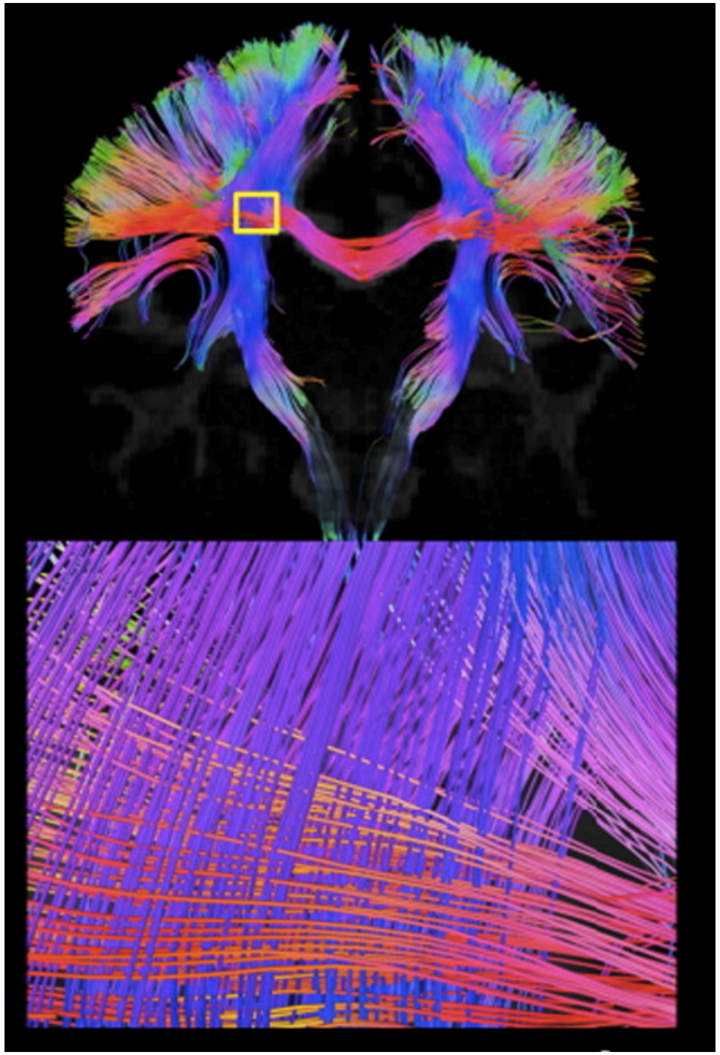
Rich-club hubs (blue)

Modules (red)

Van den Heuvel & Sporns (2013). JNeurosci.

Brain networks in humans – data

- Multiple data-sharing efforts using **large subjects**
- Functional data: **resting state/task fMRI & MEG** (e.g. human connectome project: 900 subjects with fMRI and 500 with MEG) http://www.humanconnectome.org/data/
- Structural data DSI: http://www.humanconnectomeproject.org/data/
- Many initiatives also for various **mental disorders** (Autism, Alzheimer's Disease, Schizophrenia, ADHD) [usually MRI and fMRI]



PART 3
Brain networks
Challenges

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1D – Space

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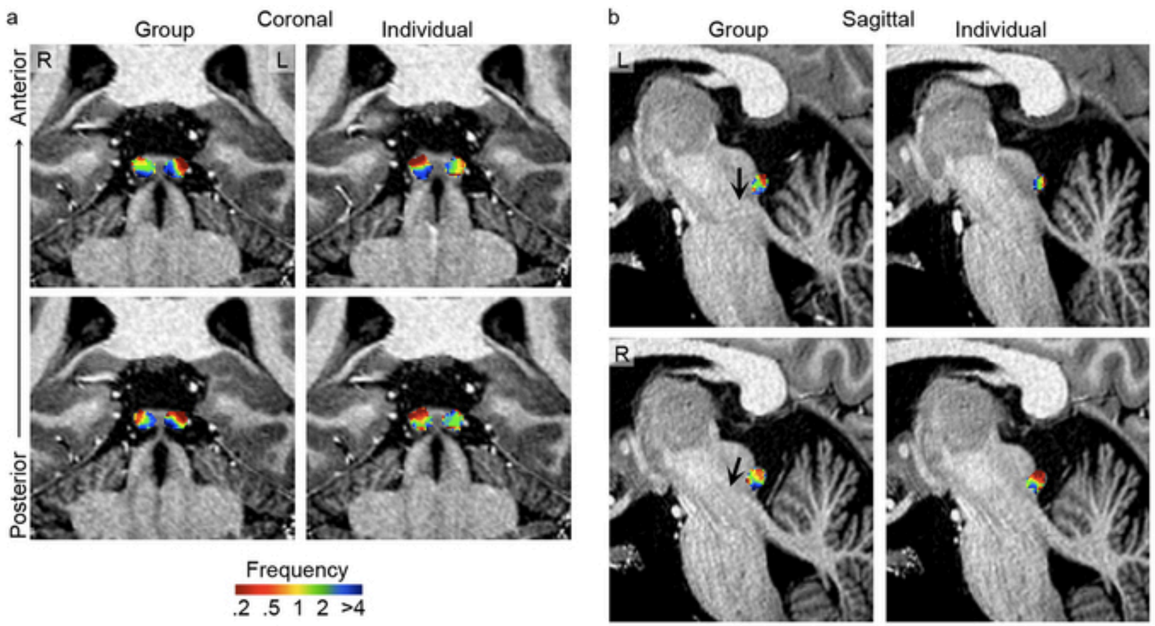
What is a node?

- Many are happy to assume that a node is
  - *A region of interest identified histologically or from another dataset*
  - *A region where the signal of neighbour voxels is more similar (i.e. dimensionality reduction e.g. via ICA)*
  - *A single voxel*

More powerful scanners (7T) -> higher SNR -> single voxels will be more and more important



Moerel et al (2015) Processing of frequency and location in human subcortical auditory structures SciRep

The spatial resolution challenge

- How to build the network?
- More nodes -> exponential growth of the network
  - *6x6x6mm voxels -> ~6000 nodes -> ~18e6 undirected connections [manageable]*
  - *4x4x4mm voxels -> ~17000 nodes -> ~130e6 undirected connections [huge memory]*
  - *2x2x2mm ??? -> needs distributed computing approach*
- Novel methods are using distributed computing:
  - *Freeman, J., Vladimirov, N., Kawashima, T., Mu, Y., Sofroniew, N. J., Bennett, D. V., ... & Ahrens, M. B. (2014). Mapping brain activity at scale with cluster computing. Nature methods, 11(9), 941-950.*
- How to deal with storage? Storing all the links? Where to draw the line?
- Network scientists should work with neuroscientists starting from the modelling of the time series/network.

2D – Individuals

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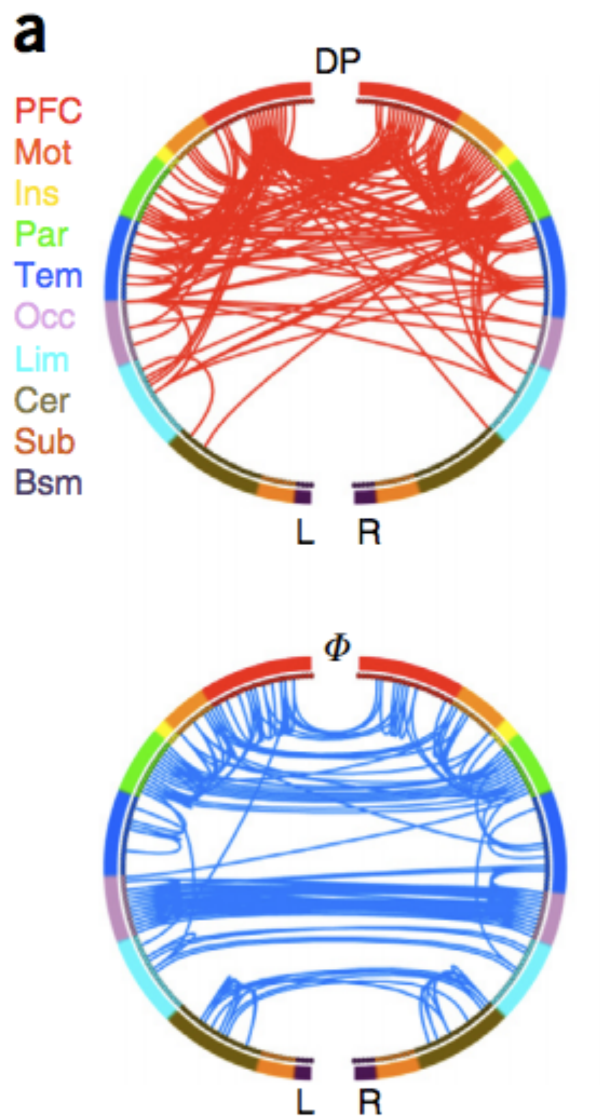
The average brain

- As a first step, it is informative to look at the **average brain**
- However the **average brain does not actually exist**
- **Variability** between individuals and on the same individual over time
- First efforts
  - *Machine learning: fingerprinting of brains*
  - *Large scale modelling (canonical correlation) between individual behavioural variables and connectivity patterns*
  - *Comparing network of individuals at brain level vs behavioural vs phenotypical etc*

Connectivity fingerprints

- Red links: highly unique
- Blue links: highly consistent

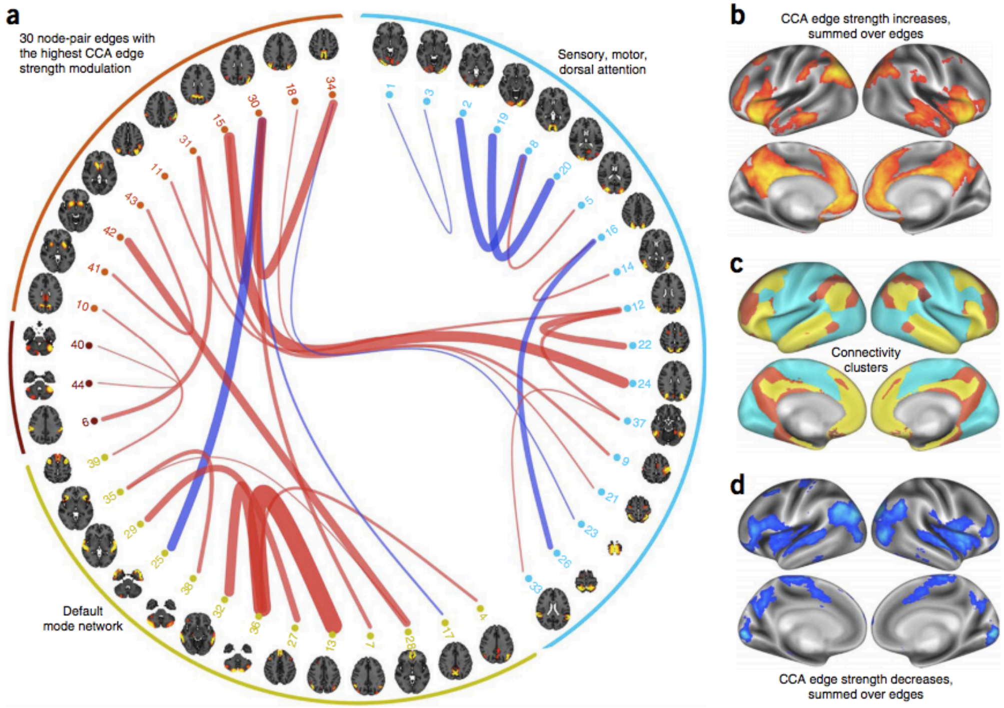
Finn, E. S., Shen, X., Scheinost, D., Rosenberg, M. D., Huang, J., Chun, M. M., ... & Constable, R. T. (2015). **Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity.** Nature neuroscience.



Matching individual traits with connectivity

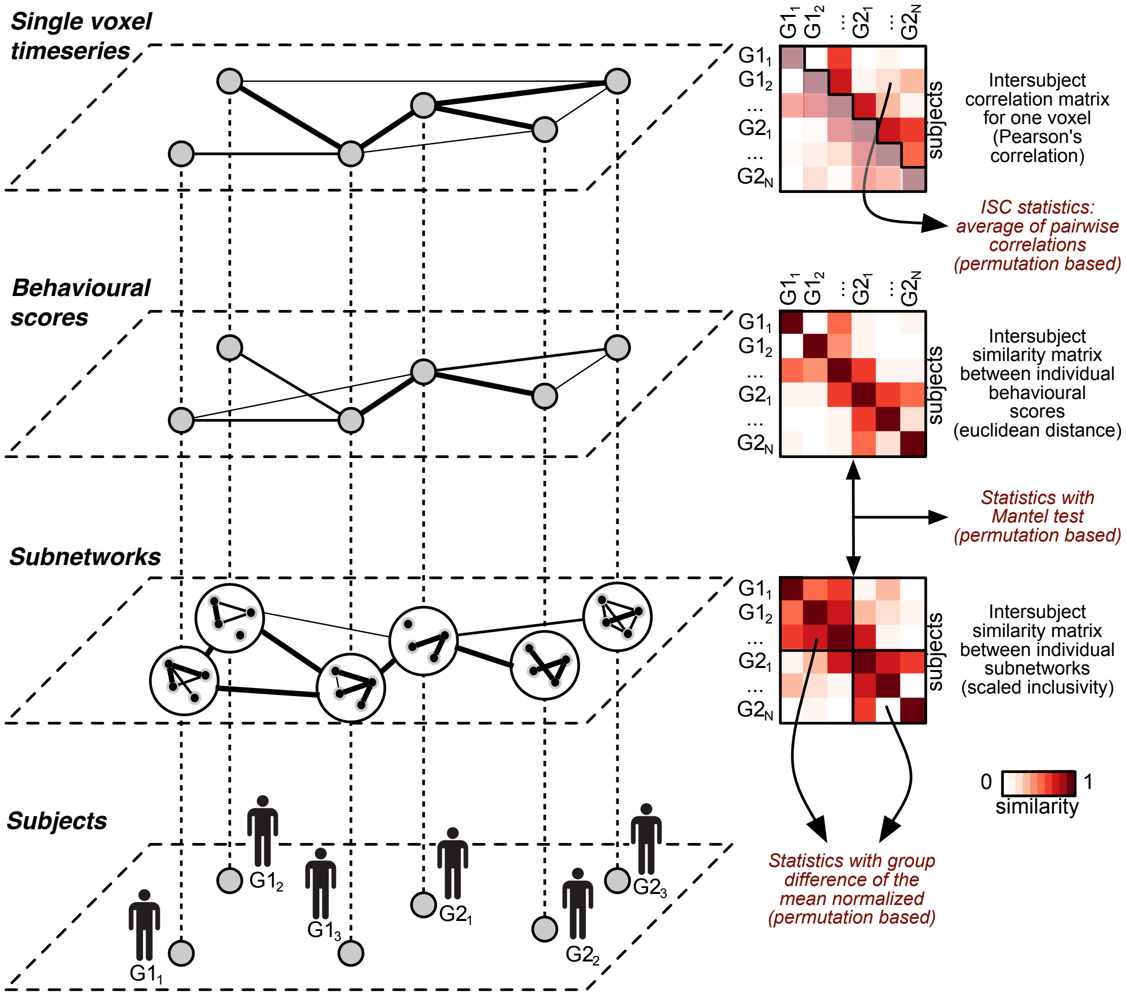
- 461 resting subjects
- 158 variables
  - *(age, gender, income, IQ, smoking habits, etc)*
- ‘Good’ and ‘bad’ humans

Smith SM, Nichols TE, Vidaurre D, Winkler AM, Behrens TE, Glasser MF, Ugurbil K, Barch DM, Van Essen DC, & Miller KL (2015). **A positive-negative mode of population covariation links brain connectivity, demographics and behavior.** Nature Neuroscience



Intersubject analysis framework

- Networks of subjects compared across dimensions
- **Mantel test** (comparison between similarity matrices)



Glerean, E., et al. (in press) **Reorganization of functionally connected brain subnetworks in high-functioning autism** Human Brain Mapping.

2D – individuals: mental health

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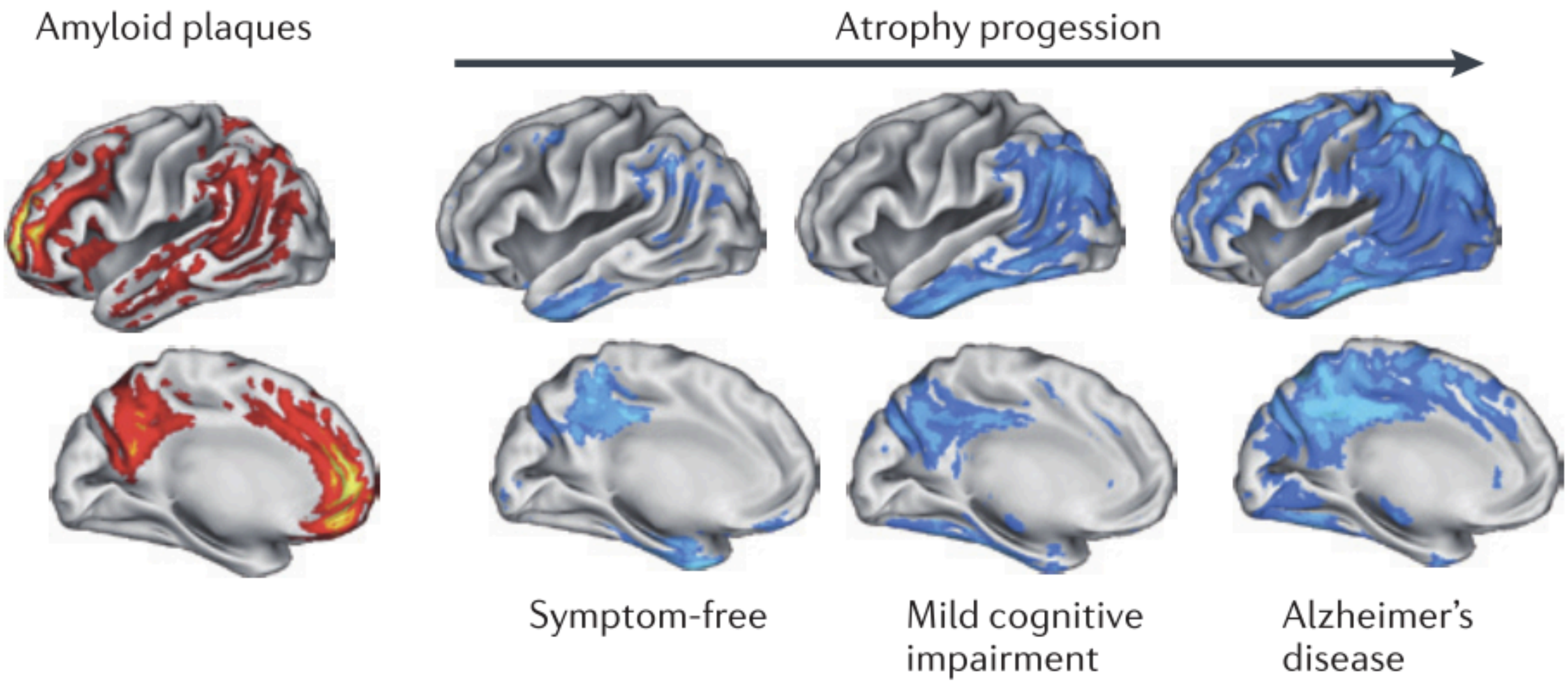
Alzheimer's disease

- **The most expensive hubs are attacked by the disease**

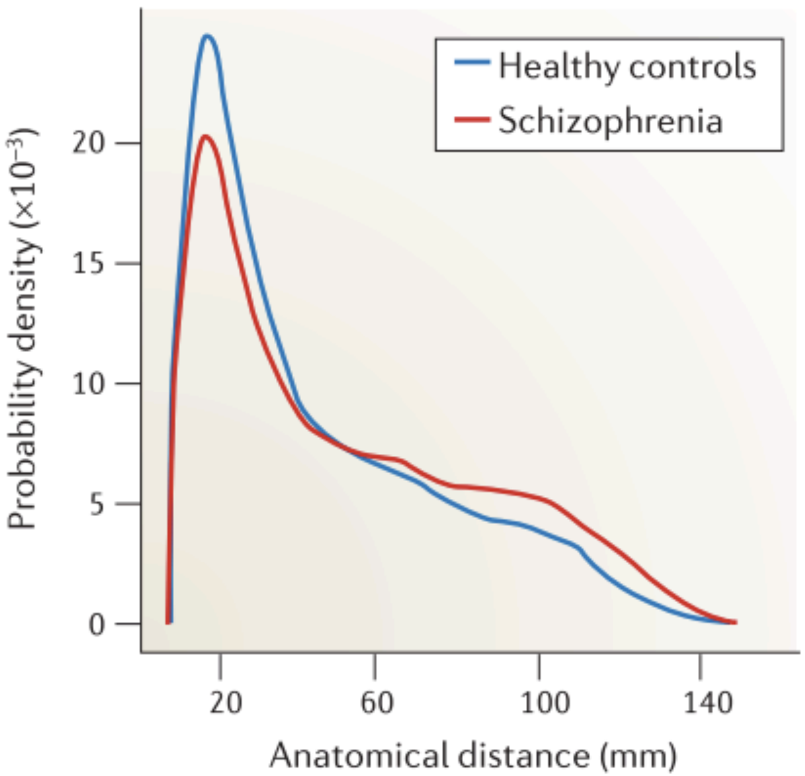


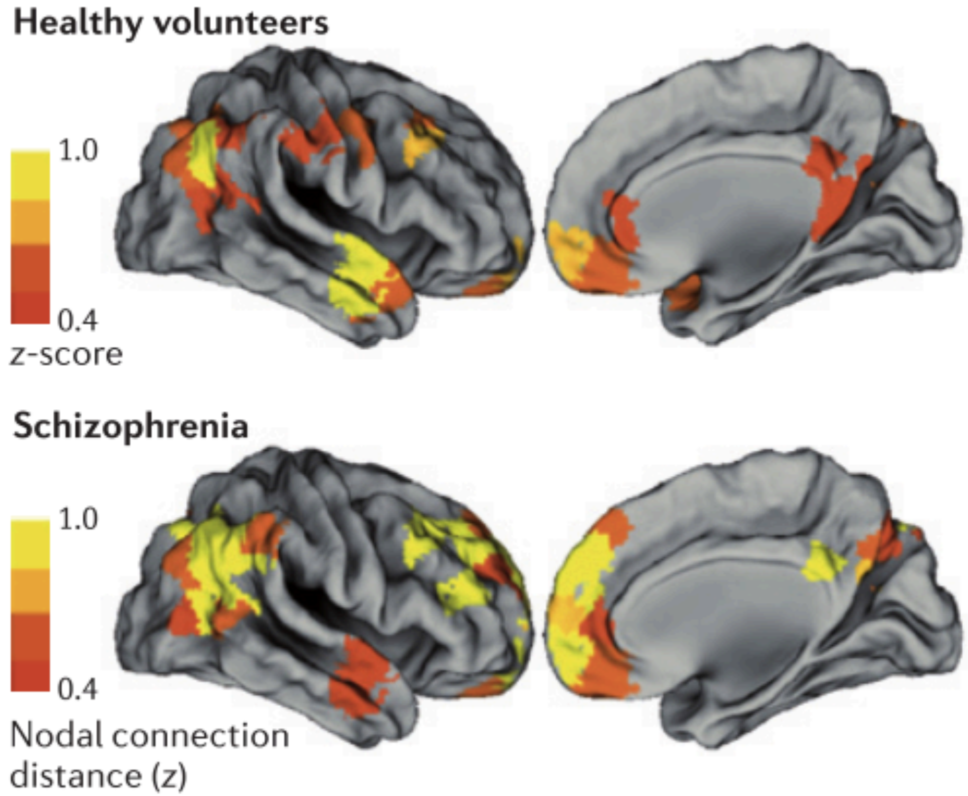
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49

Schizophrenia

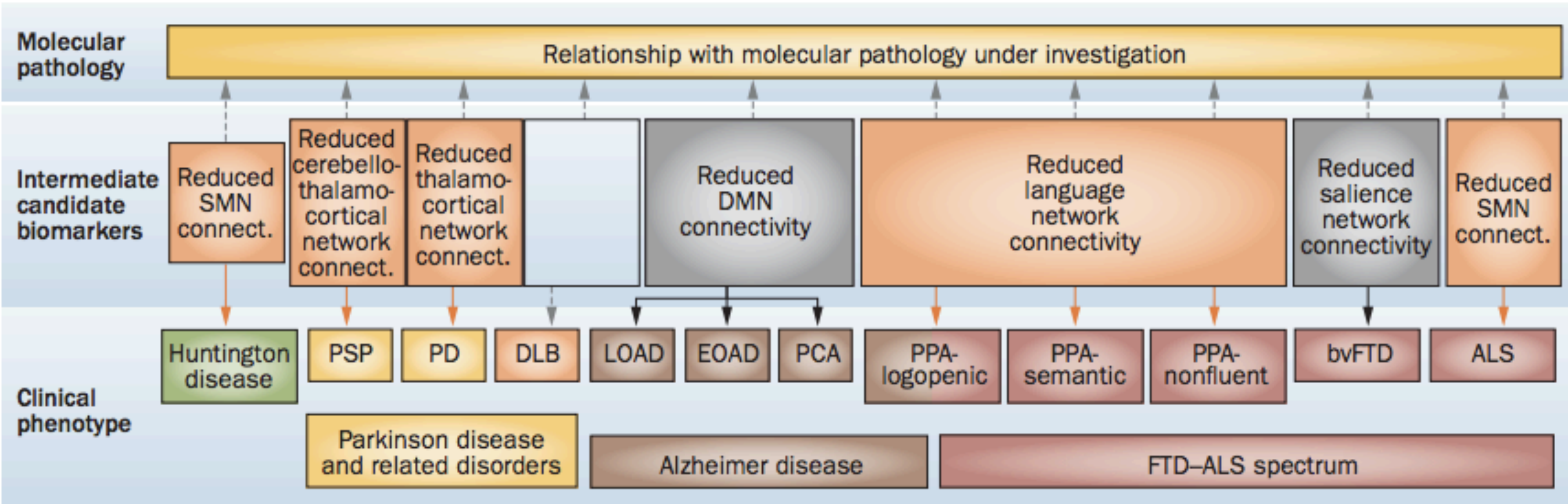
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization.

- **Unbalanced small-worldness**





Brain networks as biomarkers



Pievani, M., Filippini, N., van den Heuvel, M. P., Cappa, S. F., & Frisoni, G. B. (2014). Brain connectivity in neurodegenerative diseases [mdash] from phenotype to proteinopathy. Nature Reviews Neurology, 10(11), 620-633. Chicago

How to deal with individuality?

- Other **approaches**?
- **Dimensionality scaling** (machine learning, ICA, subnetworks) is still a big limiting decision
- Modelling **noise vs signal**?
- It adds on top of the **other challenges** (especially on how to build the network)
- Healthy vs **clinical** groups

3D – Imaging modalities

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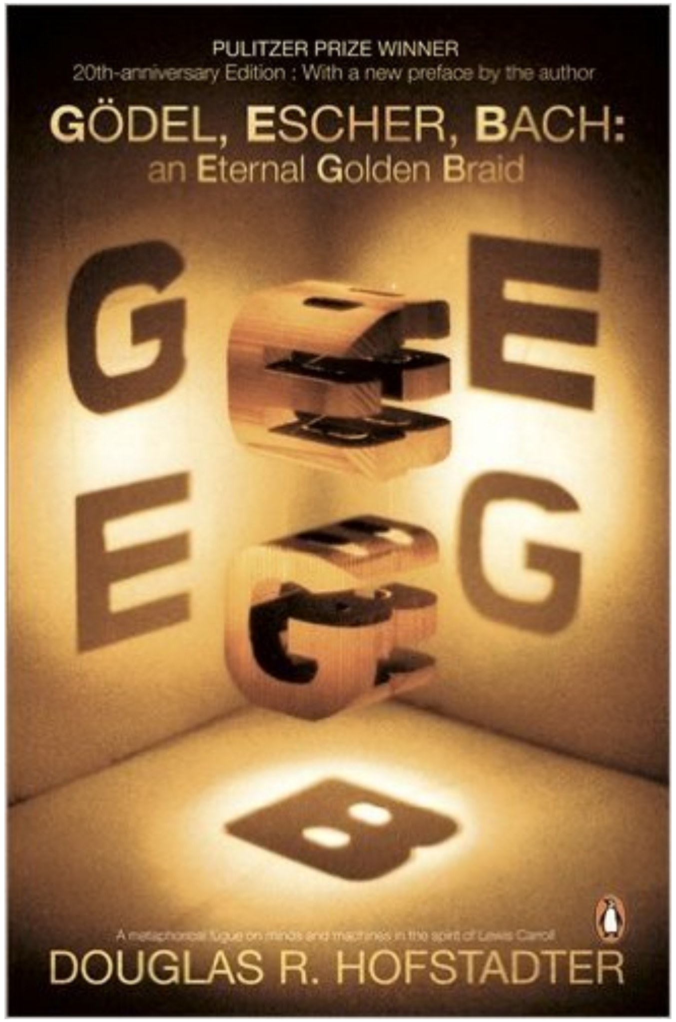
Brain networks across modalities

- Multiple imaging modalities
- Is it the same object projected over different planes?
- **Integrating modalities**



Brain networks across modalities

- Successful efforts of integrating
  - ***fMRI***
  - ***M/EEG***
  - ***DTI/DSI***
  - ***MRI***
  - ***Computational models***

  Reference list is long, I can email
- Upcoming efforts of linking **PET** with DTI/DSI and functional connectivity

Different modalities present different assumptions and artefacts

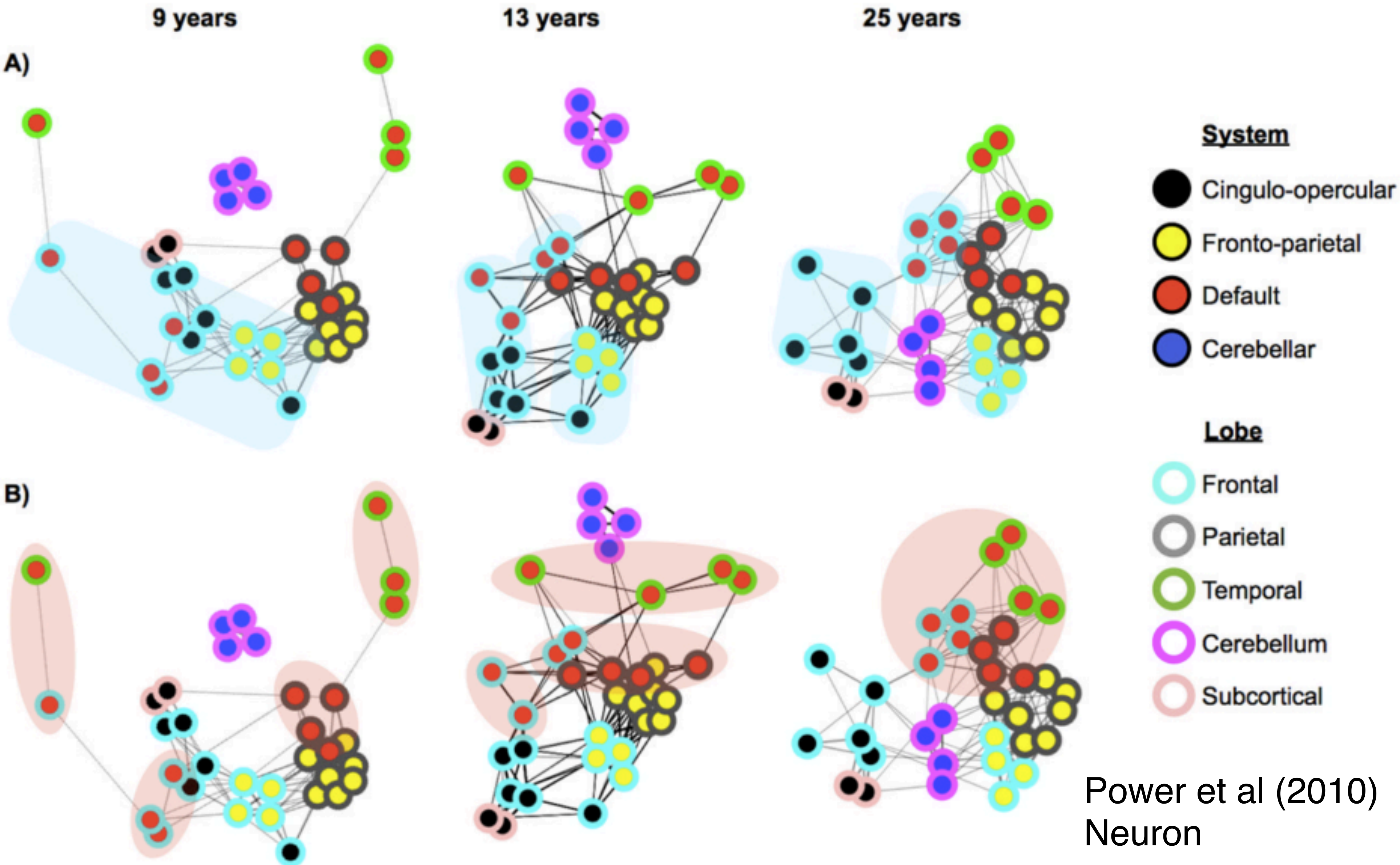
- How to **combine** all the types of networks from **same subject**?
- How to use one modality as ‘prior’ knowledge for another modality?
- How to summarize properties that generalize across modalities (or not!) [multiplex networks?]

4D – Time

Brain networks in time

- At ms scales: interesting works works with MEG
- At second scales: sliding window connectivity and other measures
  - *Lots of disagreement in the field*
- Repeated measures for a single subject
  - *My connectome project http://myconnectome.org/wp/ same subject scanned ~100 times*
  - *Some measures are stable some other covary with time of the day, time of the year etc.*
- Work across age groups (e.g. the developing brain)

Network changes from childhood to adulthood



Power et al (2010) Neuron

Brain networks in time

- First we need **meaningful methods to estimated meaningful temporal networks**
- Can novel **advances in the network science of temporal networks** help neuroscientists?
- How to integrate temporal measures **across imaging techniques**

5D – Networks of networks

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Two persons neuroscience

- We interact with eachother and our brain network activity influences others' brain networks activity
- Modelling a network between the two networks
- This network will not have usual properties (e.g. lower significance of strength of connections)
- How to model this? Bi-partite network? [so far I have been using permutation based approaches]

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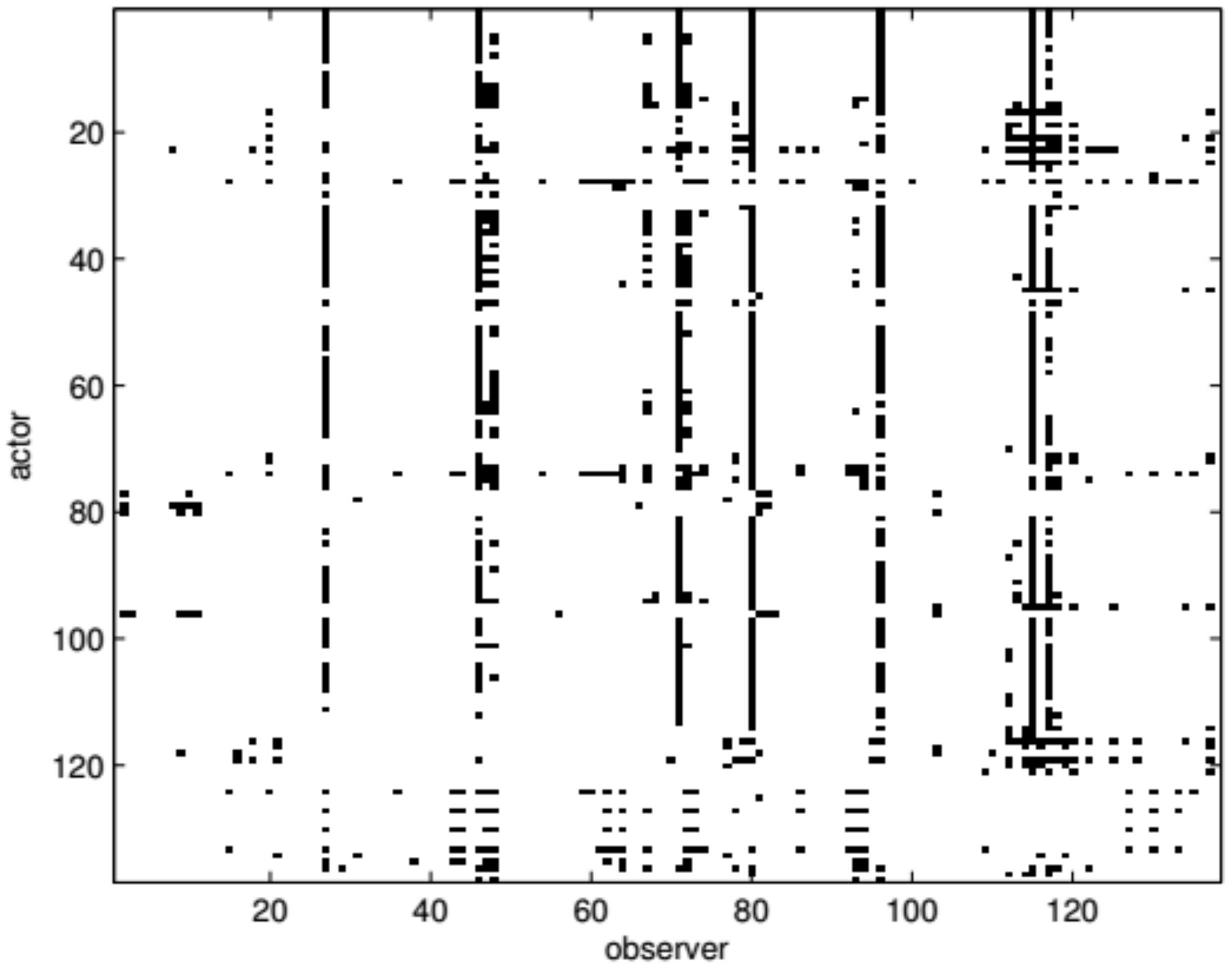
Two persons neuroscience



Conclusion

Summary of challenges

- 1) **space** (increasingly larger networks due to higher quality of data)
- 2) **individual variability** (individual subjects with individual phenotypical/behavioral/genetic/clinical variables versus group averages)
- 3) **imaging modalities** (integration of multiple modalities/types of data such as structural MRI, functional MRI, M/EEG, PET, DTI/DSI, modeling, etc)
- 4) **time** (networks evolving in time at ms/seconds/hours/years temporal scales)
- 5) **networks of networks** (two-persons neuroscience)

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Brain networks Current state and future challenges

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