Location, Location, Location!

Homological scaffolds and gene mapper
Application to neuroscience

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WCNTDA, UKM, 25th September 2019

CMPH
Centre for Mathematics of Precision Healthcare

Imperial College London

ISI Foundation & ISI Global Science Foundation

NIHR | Imperial Biomedical Research Centre

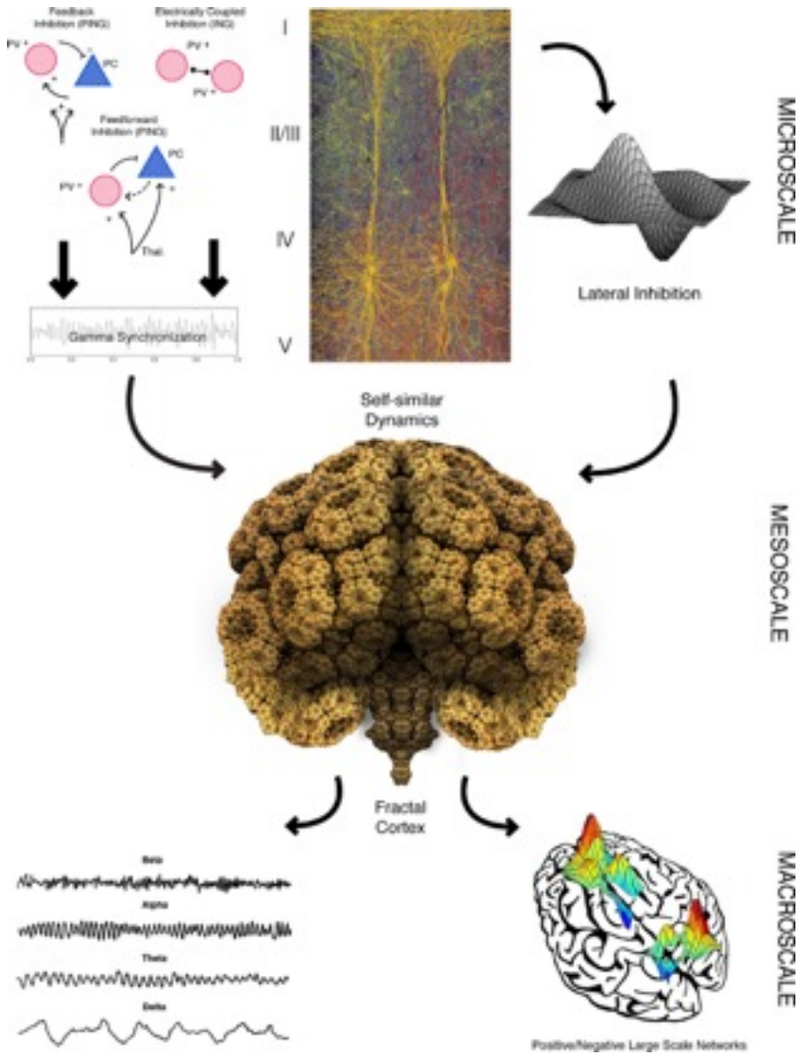
The « so what ?» question

A synergy between new methodology and « clinical » questions is needed.

How to relate, i.e. validate, new findings with existing knowledge while providing added value?

New methodologies are needed:
i) to integrate large and complex data coming from different modalities, meta-data
ii) to interpret results from topological methods.

Understanding brain function: a complex multi scale problem



Different output

Same output

Same structure/function

Different structure/function

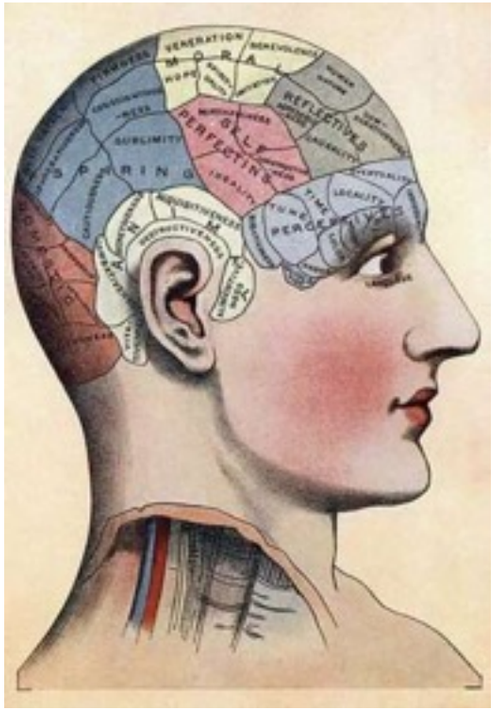
Semiology of catatonia: https://www.youtube.com/watch?v=i9zEJM_OWzE

Lord *et al.*, NeuroImage (2011); Neuroimage Clin(2012).

Turkheimer *et al.*, Neuroscience and Biobehavioral Reviews (2015).

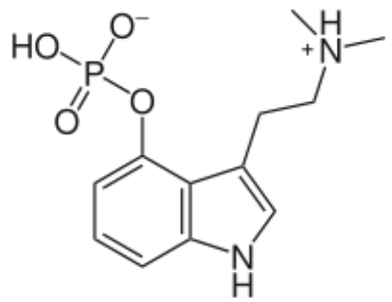
Networks/simplicial complexes

Fundamental paradigm change:
from phrenology to an integrated system.



From studying activation variance to covariance.
The importance of this representation cannot be overstated.

Altered states of consciousness: psychedelics

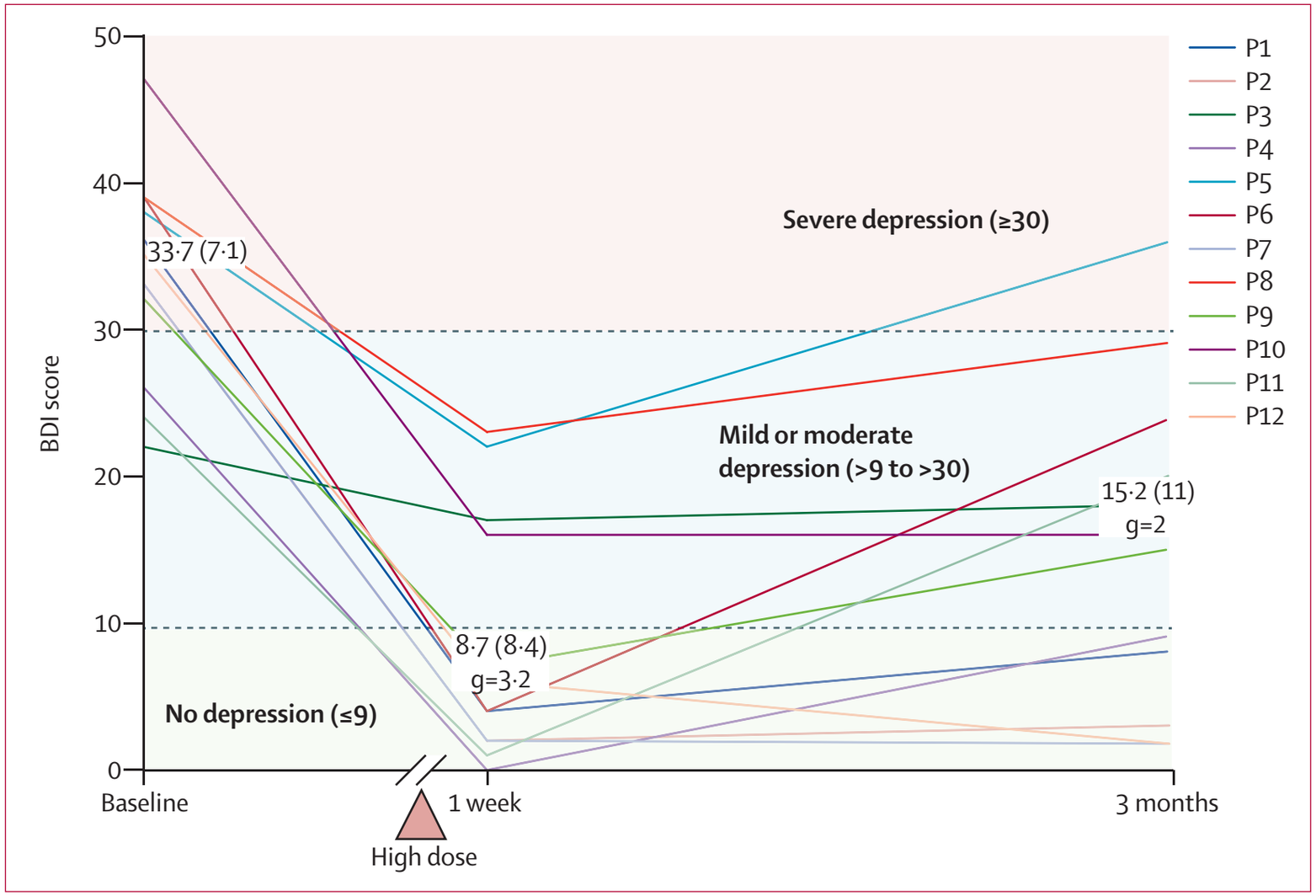


Magic mushrooms: psilocybin

THE CENTRE FOR PSYCHEDELIC RESEARCH
Imperial College London

Dr Robin Carhart-Harris

Altered states of consciousness: psychedelics



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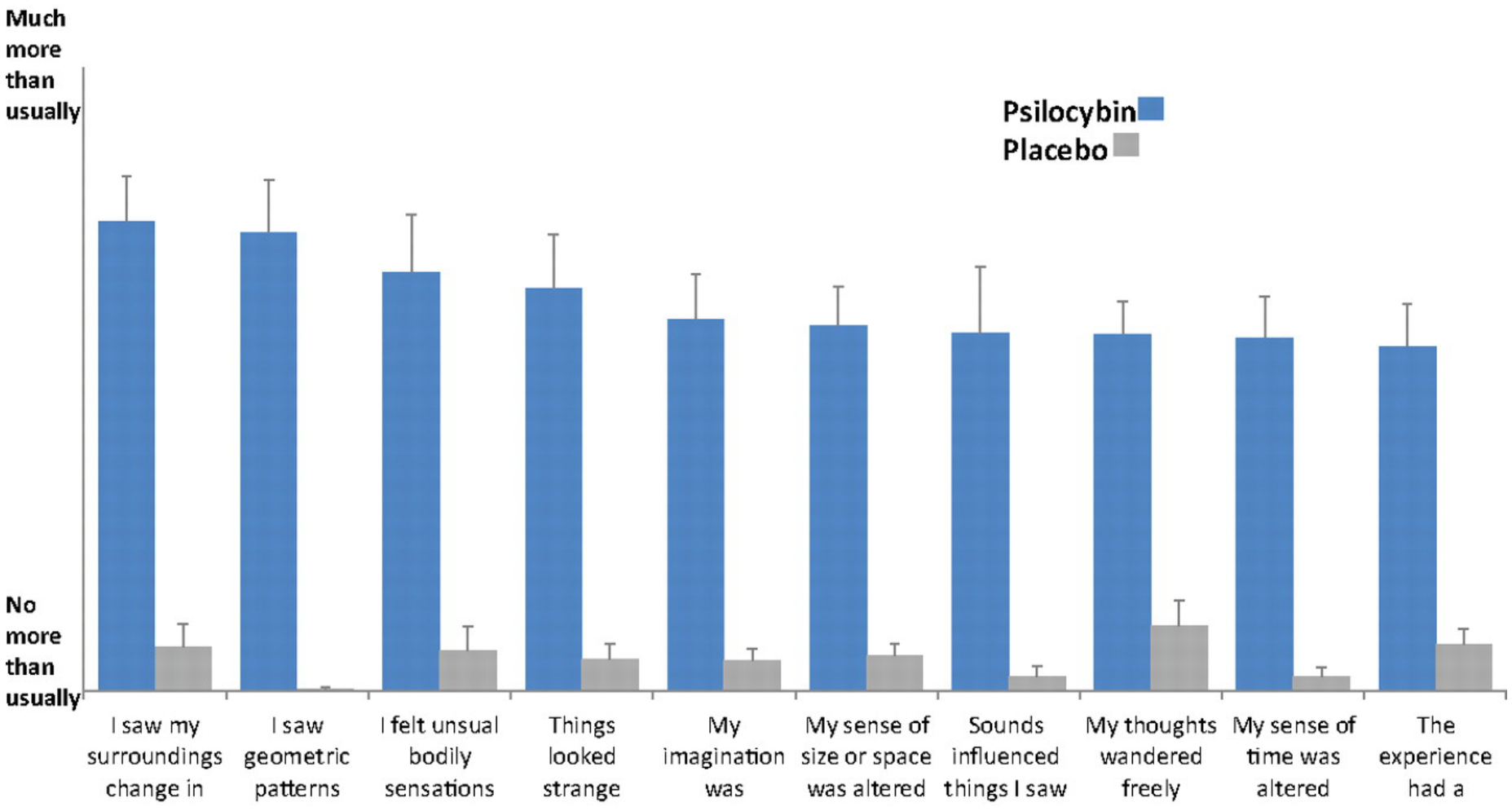
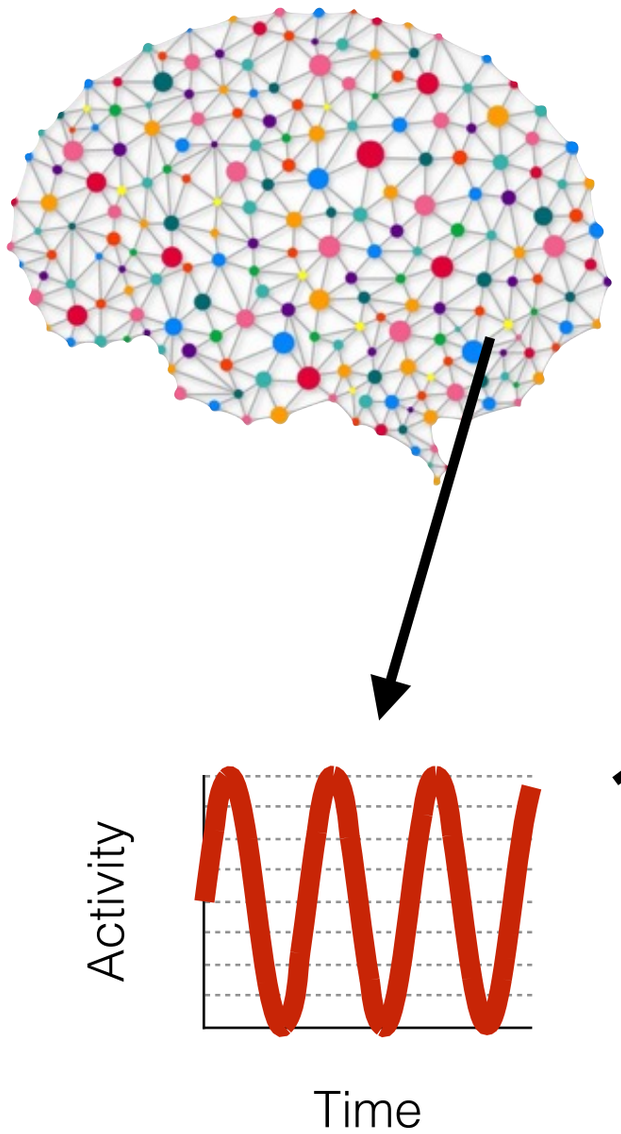
Carhart-Harris, *Lancet* (2016)

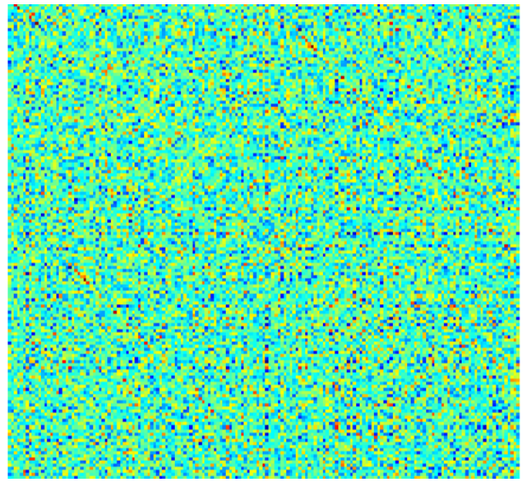
Altered states of consciousness



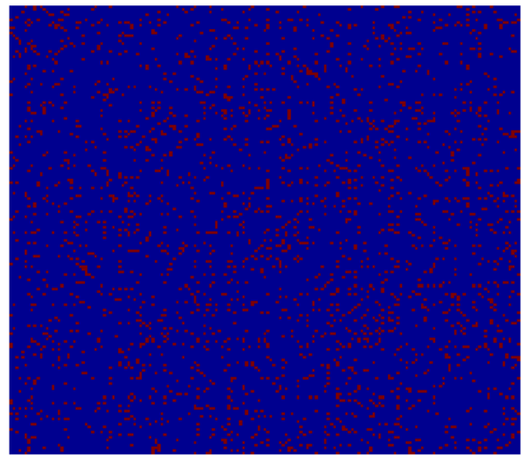
R. L. Carhart-Harris *et al.* PNAS (2012).

Functional brain network analysis: limitation





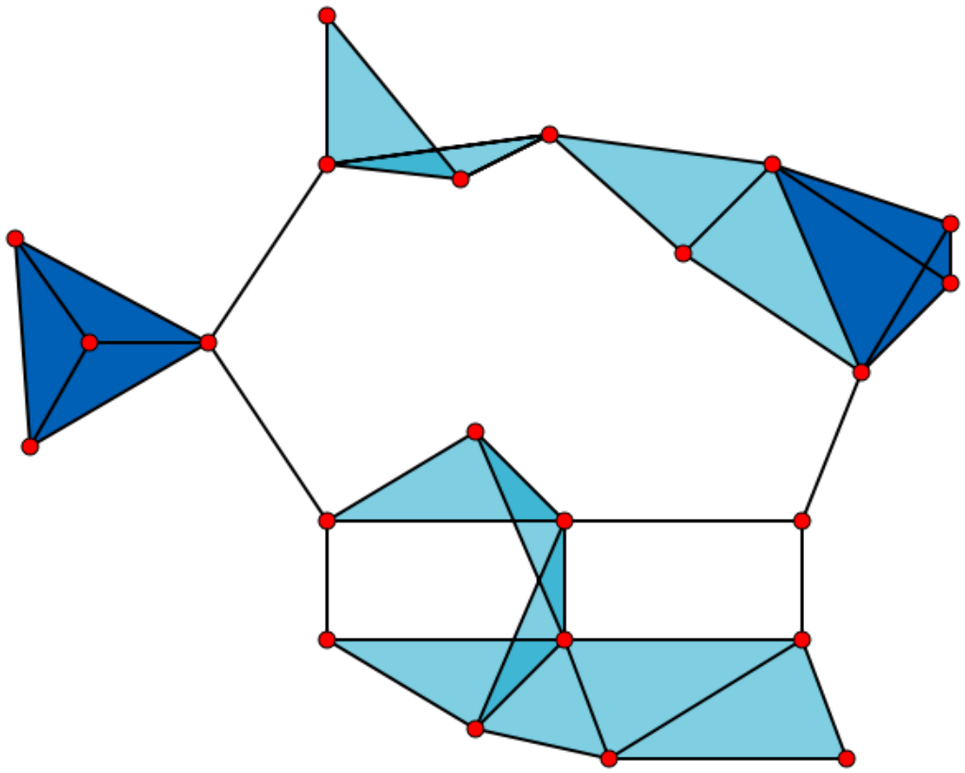
Correlation matrix



Thresholded correlation matrix

Implicit choice of interaction scale
Implicit binary interactions model

Clique complex



Cliques are set of ROIs that are all pairwise correlated above a given threshold, simplification in subunits.

New types of mesoscopic structures appear: holes.

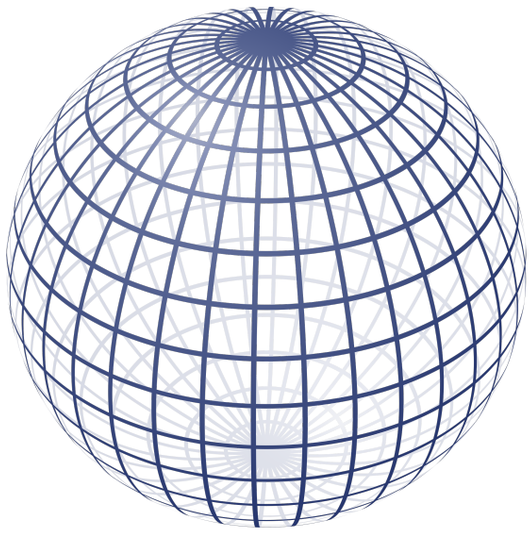
To any undirected graph *G* can be associated a clique complex *X(G)*.
A clique of size *k* is represented by a simplex of dimension *k-1*.

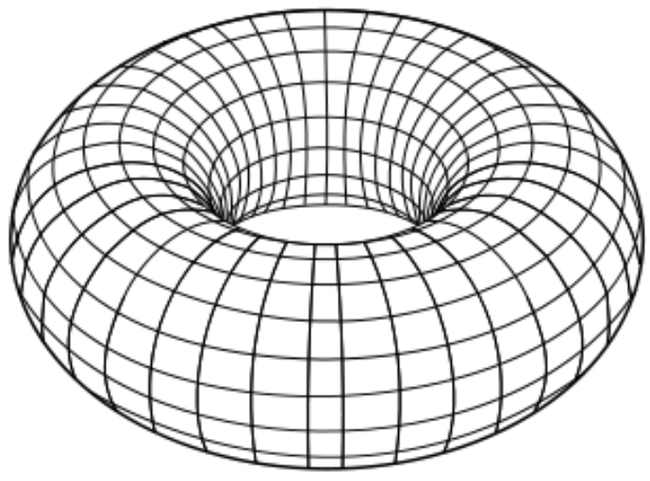
https://en.wikipedia.org/wiki/Clique_complex

Characterisation of brain function with topological invariants

Holes can be used to characterise topological spaces.
We can derive such spaces for different brain states.

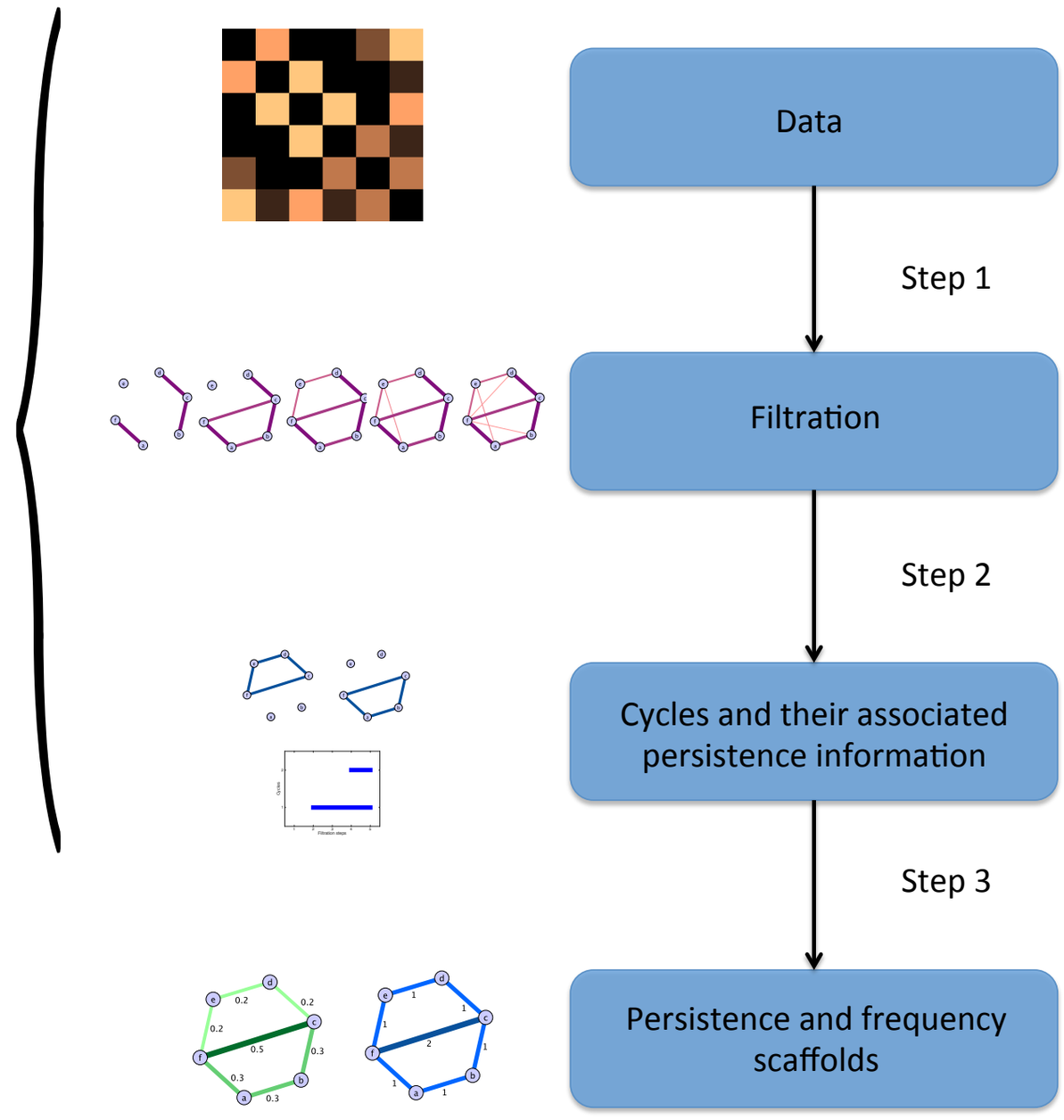
The problem of scales still remains.



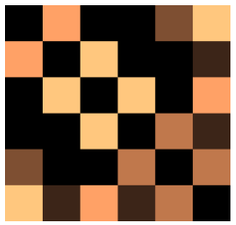


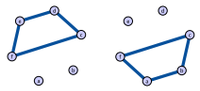
Persistent homology

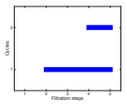
Persistent homology



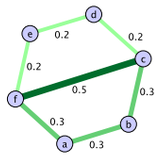
Localisation

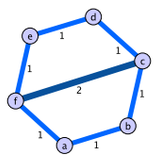






Homological scaffolds
Localisation





Data

Step 1

Filtration

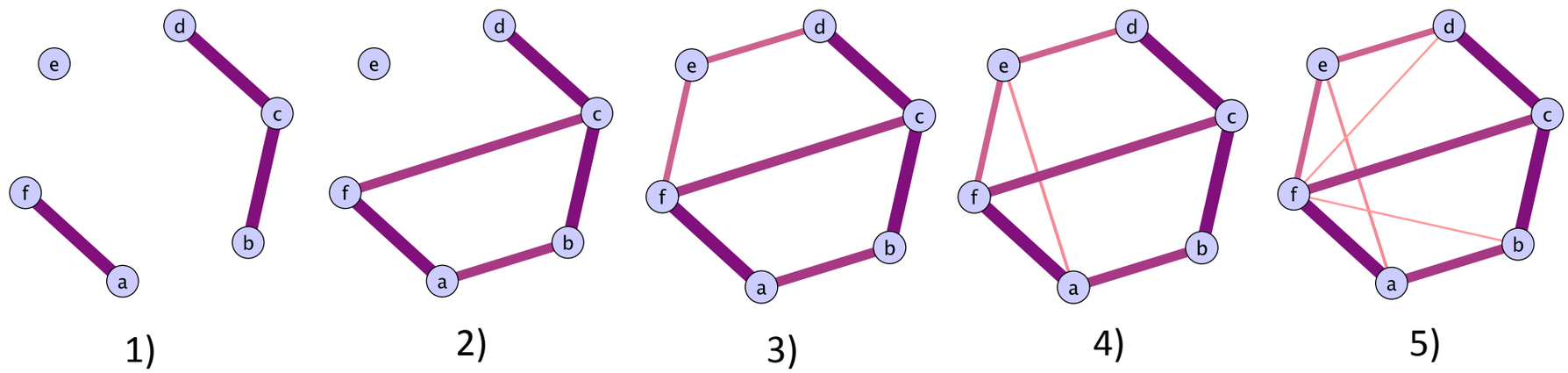
Step 2

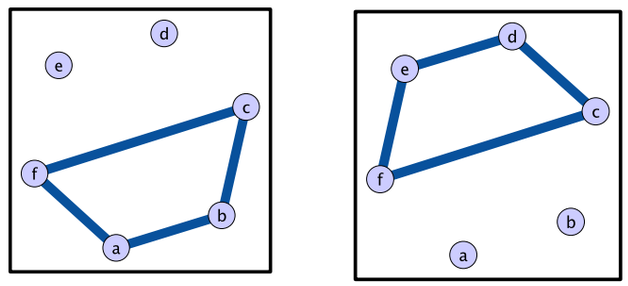
Cycles and their associated persistence information

Step 3

Persistence and frequency scaffolds

Weight Clique Rank Filtration

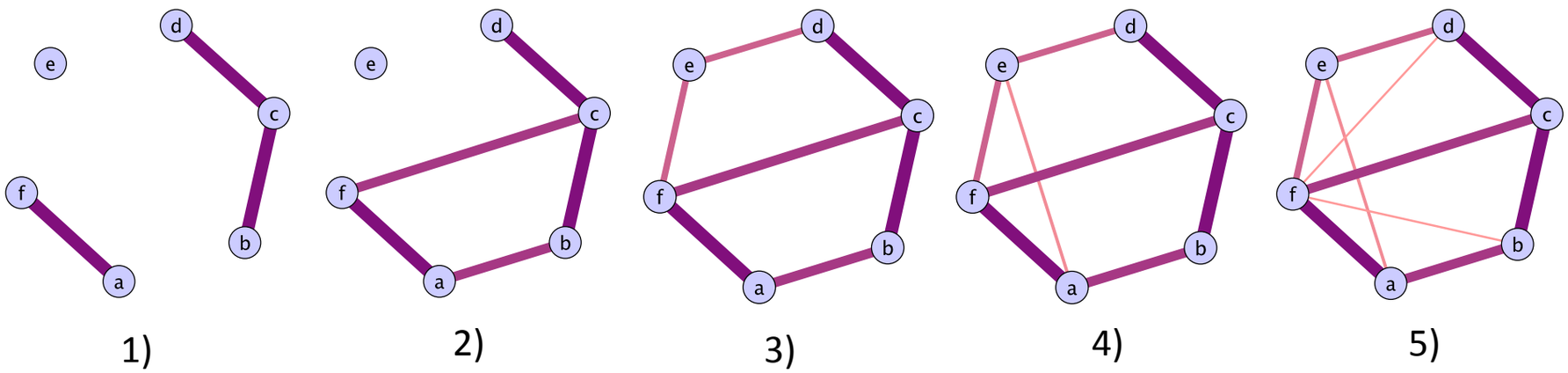


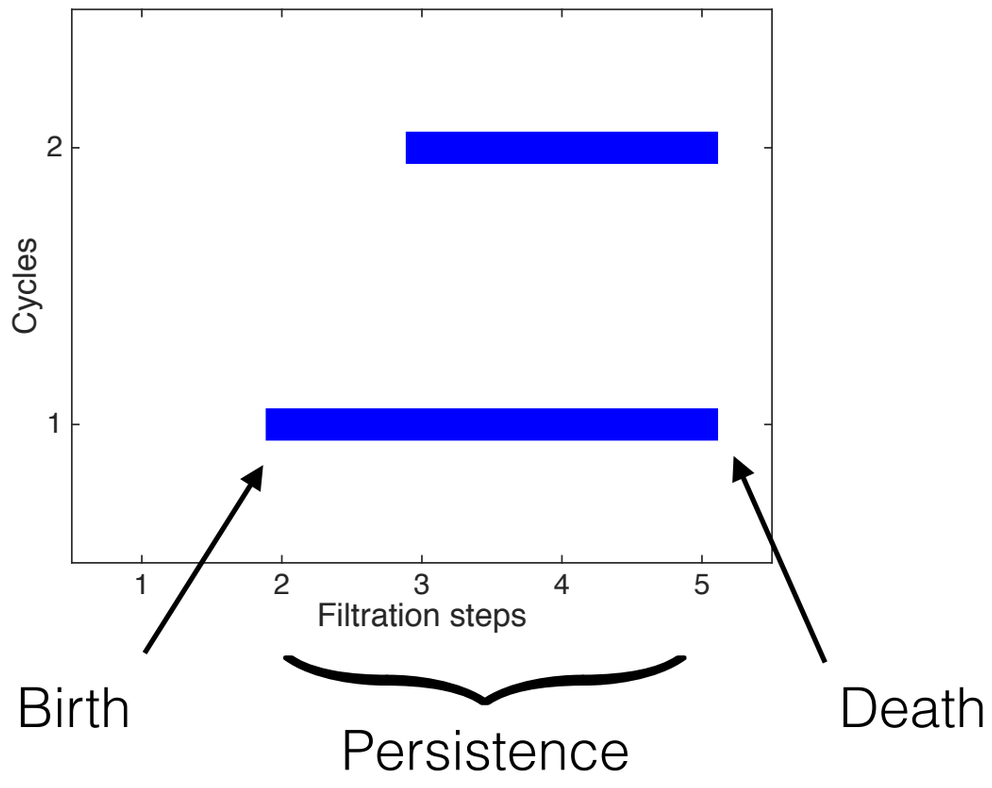


- Start with an empty network of ROIs.
- Add an edge from the correlation matrix in decreasing order of weight.
- At each step, generate the associated clique complex and compute its 1st homology group

Petri *et al.*, PLoS One (2013).

Characterisation of cycles

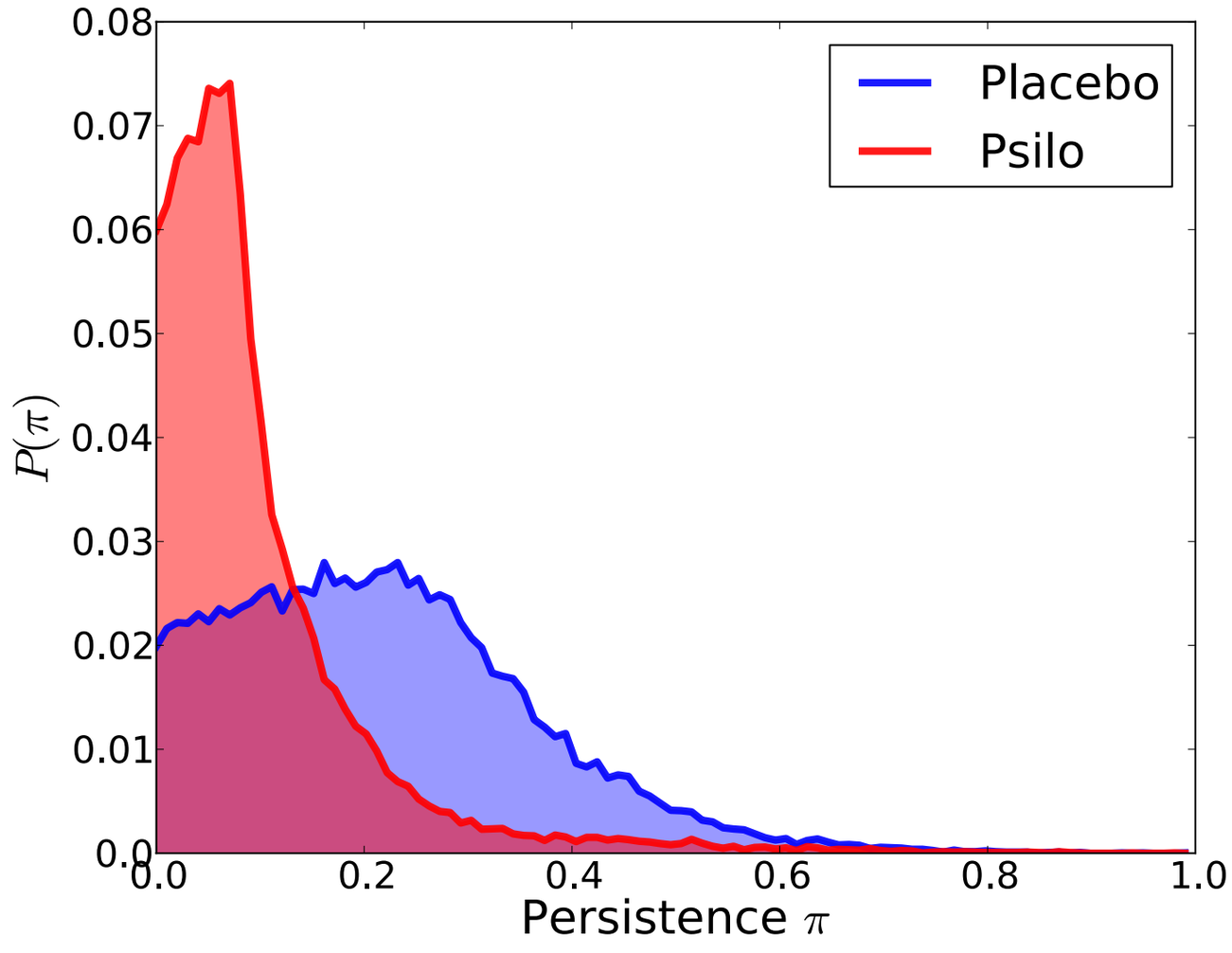




Persistence

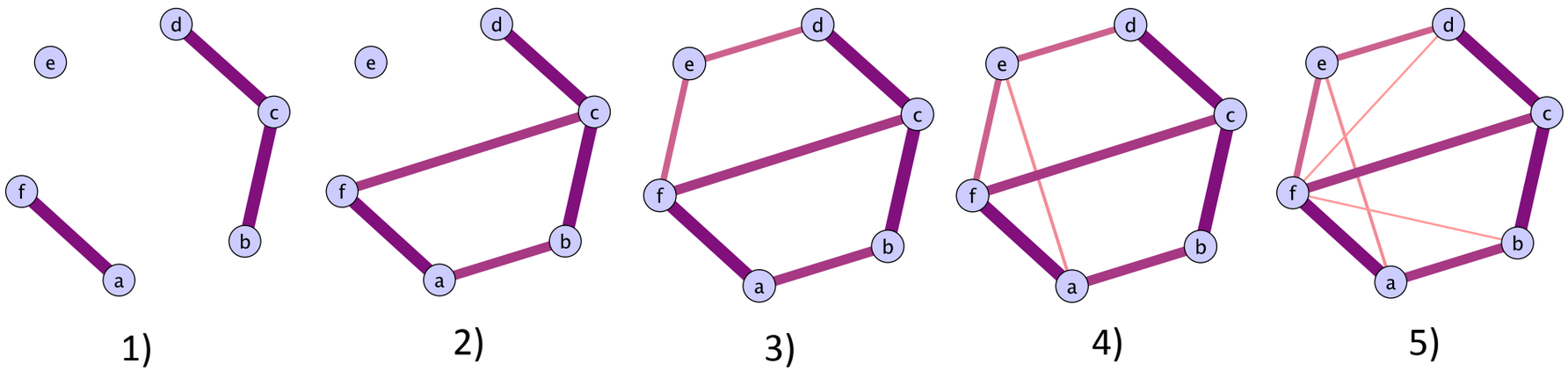
$$\pi = \delta - \beta$$

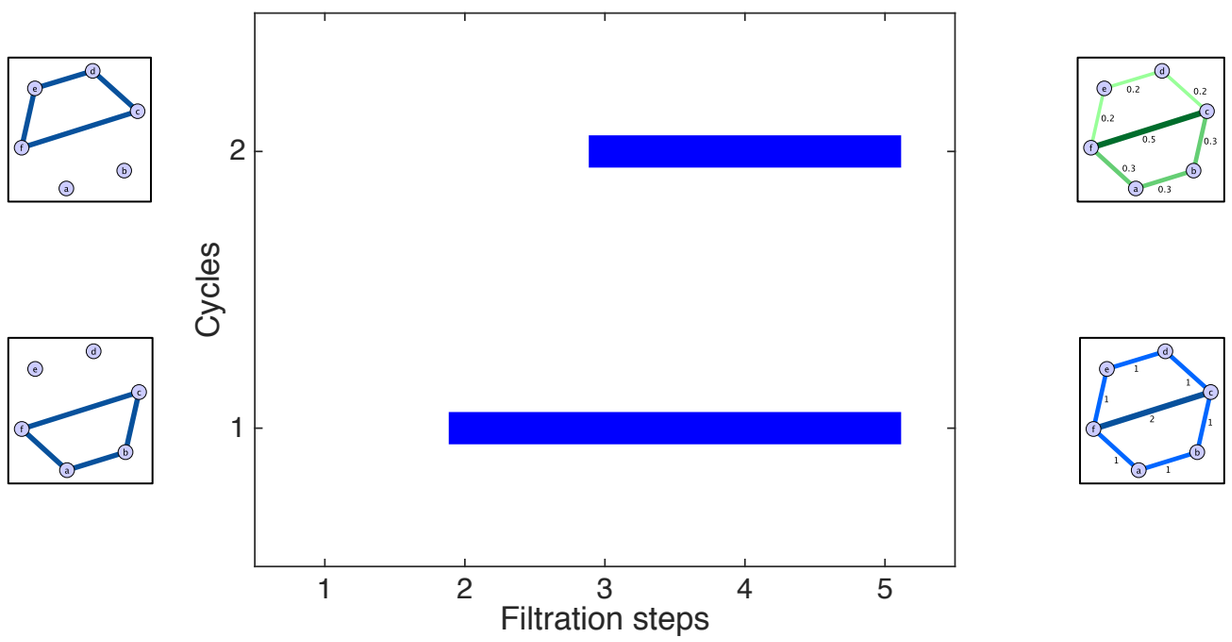
Cycles statistics



What does the average persistence tell us?

Localisation: Homological scaffolds

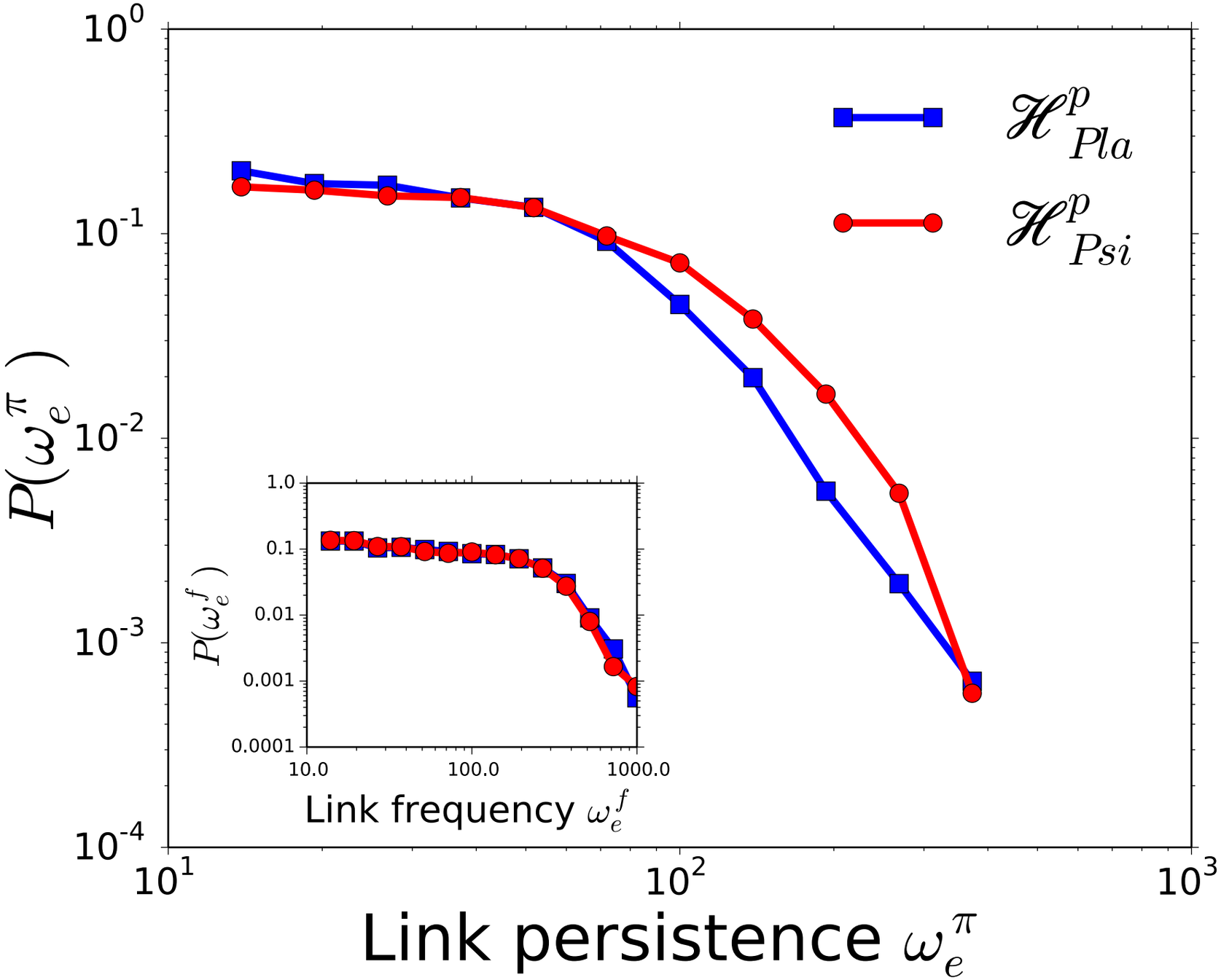




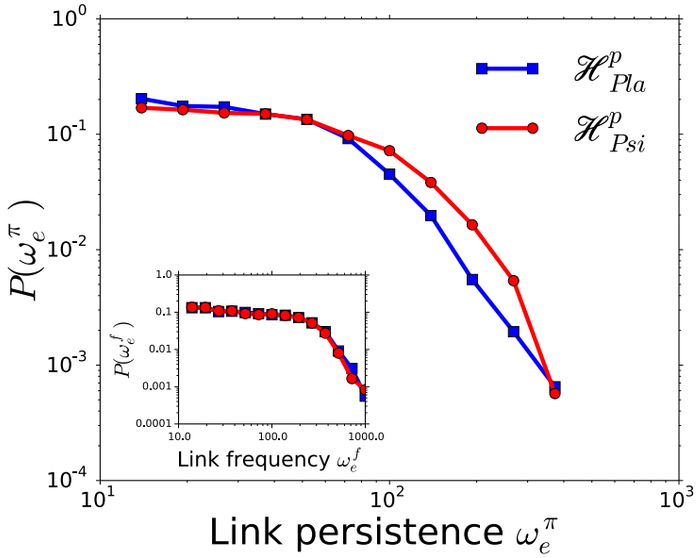
$$\omega_e^{\pi} = \sum_{g_i | e \in g_i} \pi_{g_i}$$

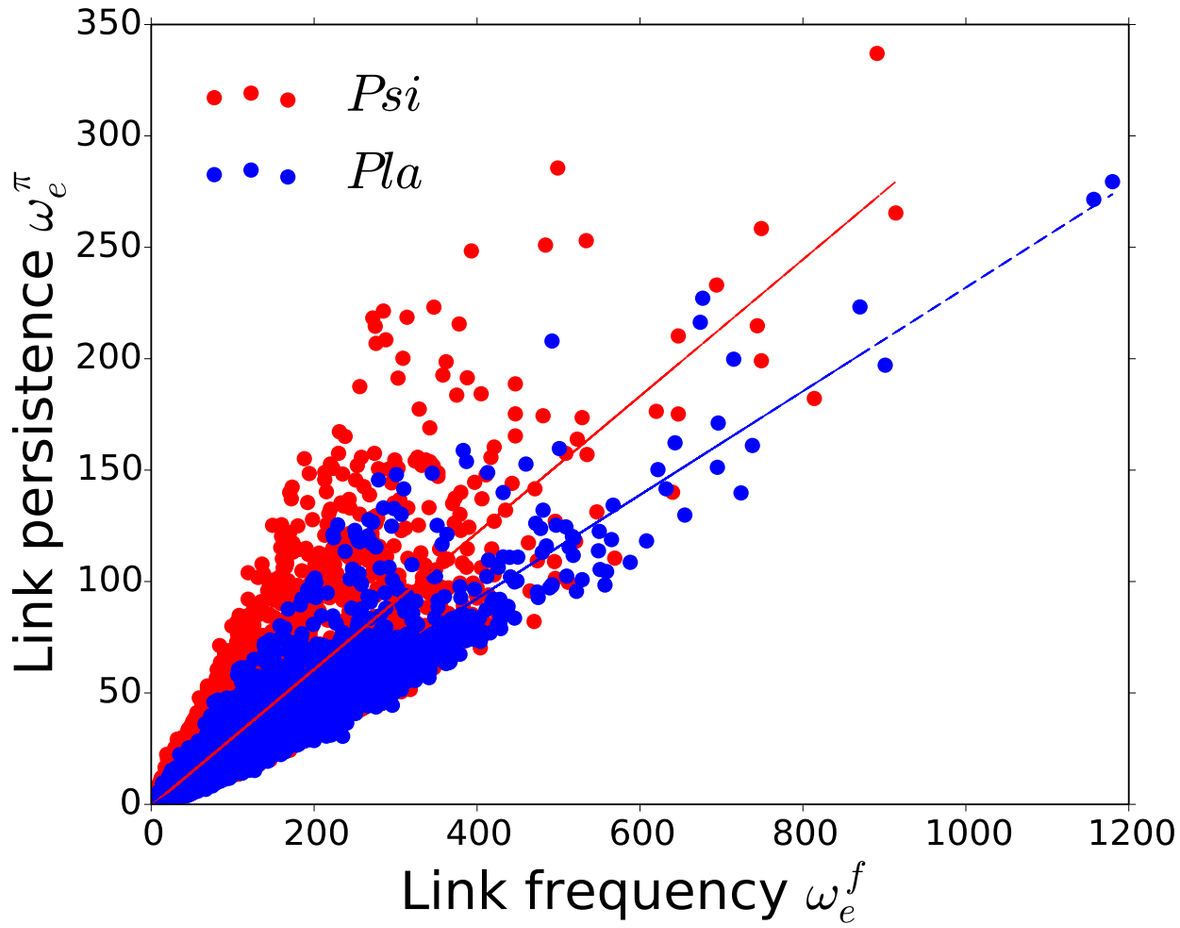
$$\omega_e^{f} = \sum_{g_i | e \in g_i} \mathbf{1}_{g_i}$$

Edge weights distributions



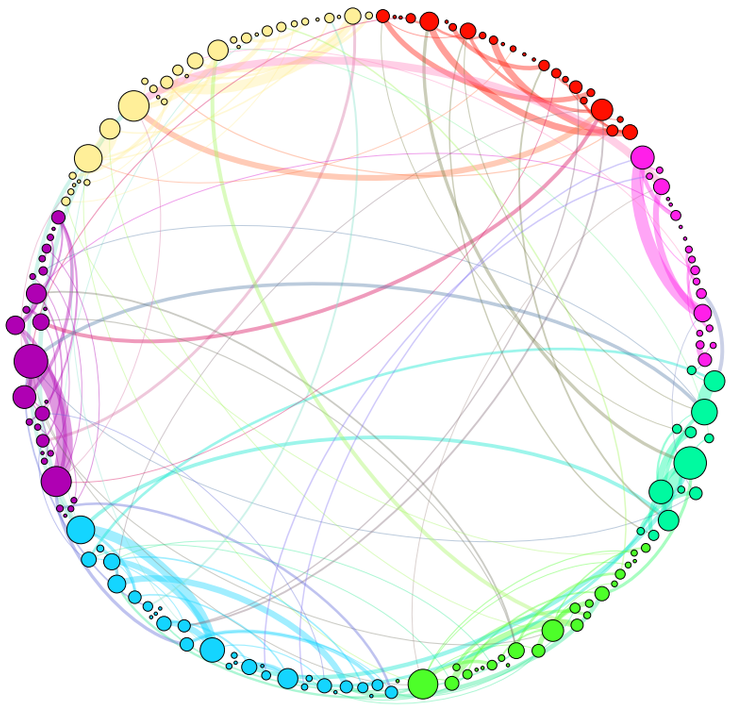
Frequency vs persistence



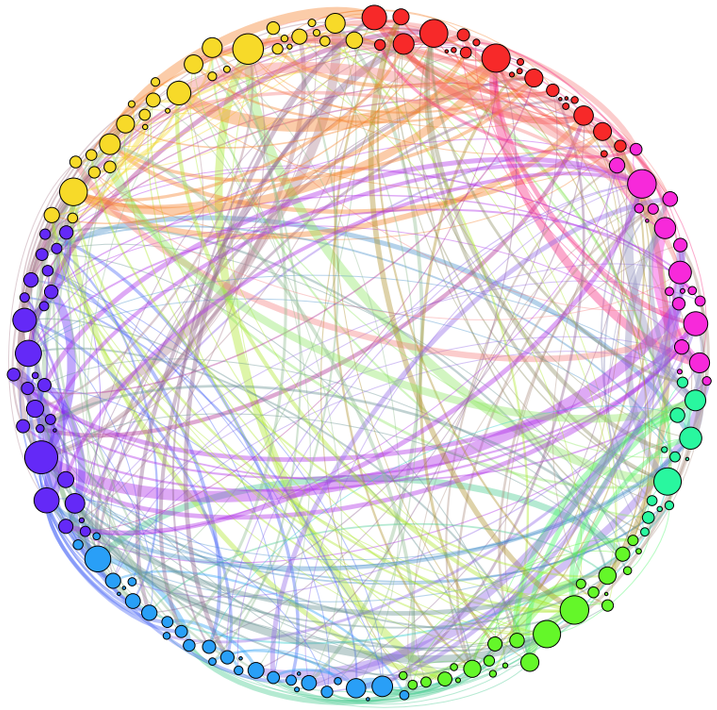


The dependence is much more scattered for the psilocybin group.

Persistence scaffolds



Placebo

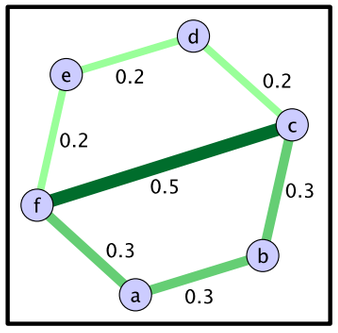


Psilocybin

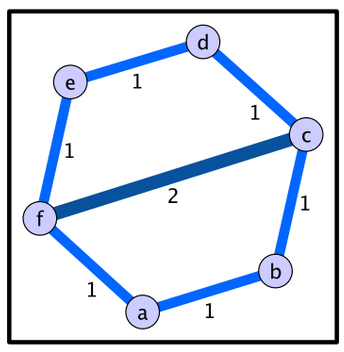
Different integration patterns.

Petri *et al.* Journal of the Royal Society Interface (2014).

Scaffolds nodes centrality



$$PSS(i) = \sum_{e \in E(i)} \omega_e^{\pi}$$



$$FSS(i) = \sum_{e \in E(i)} \omega_e^{f}$$

Represent centrally extracted from information about the holes structures.

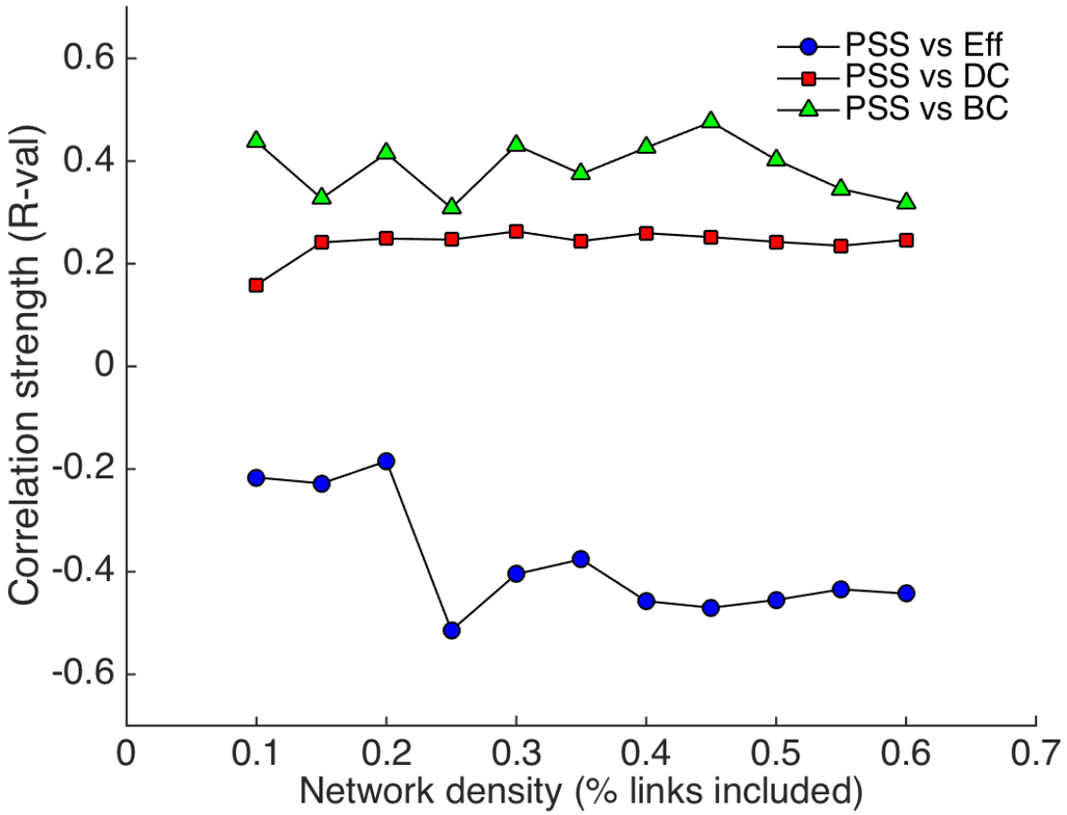
Relation between simplicial and network metrics

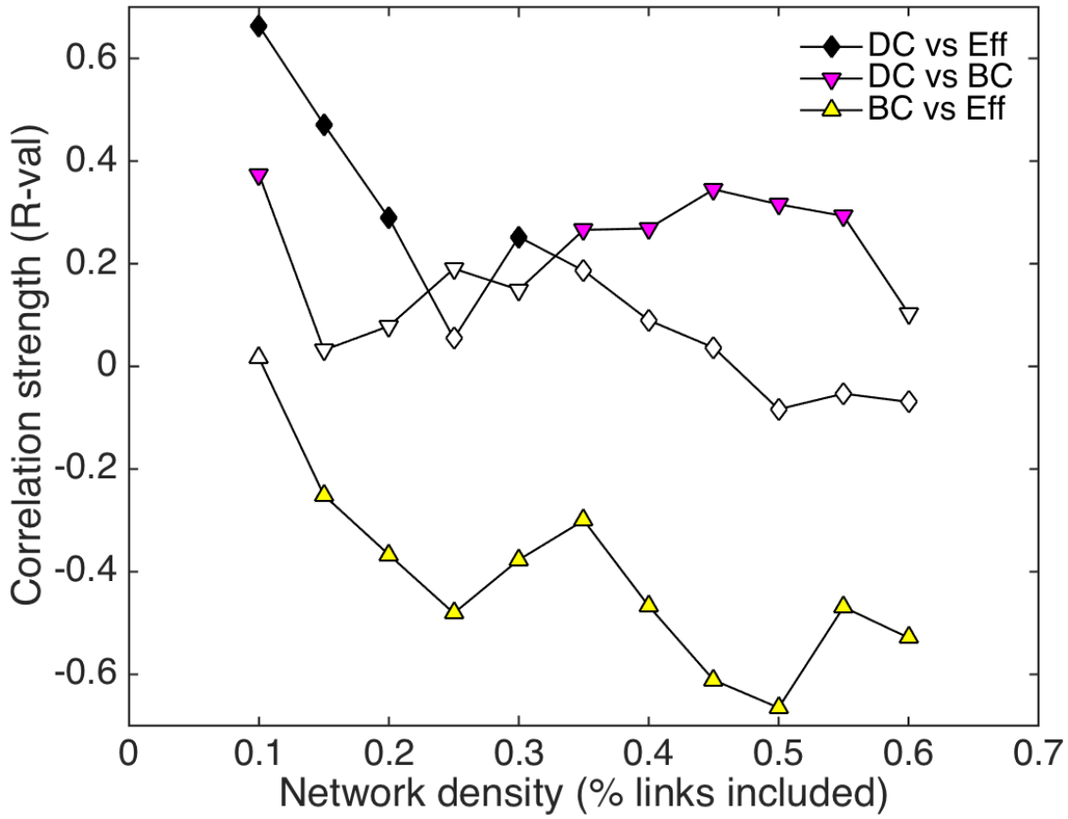
- Data: resting state fMRI time series for 90 ROIs and their associated correlation matrix.

- Persistent homology thread:
  Persistent homology with weighted clique rank filtration: homological scaffolds and the associated PSS.

- Network thread:
  Thresholding applied for a target density: Degree and betweenness centrality and efficiency computed.

Relation between simplicial and network metrics

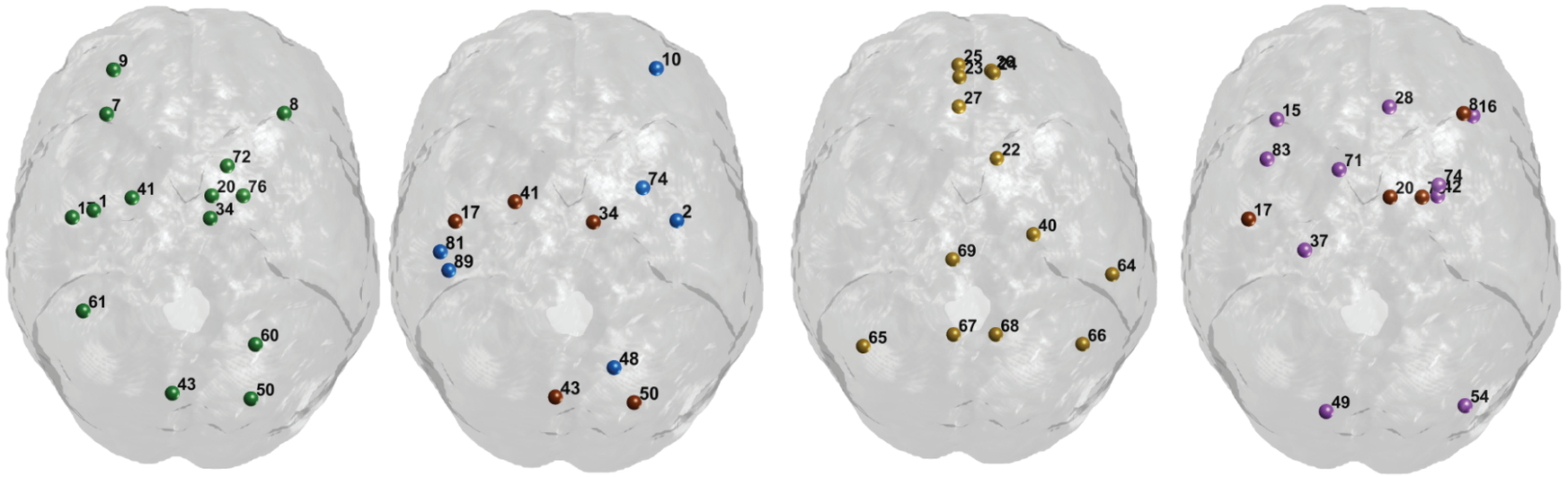




PSS naturally combines different aspects of network organisaiton, highlighting a type of integrator nodes.

Lord *et al.* Front. Syst. Neurosci.(2016).

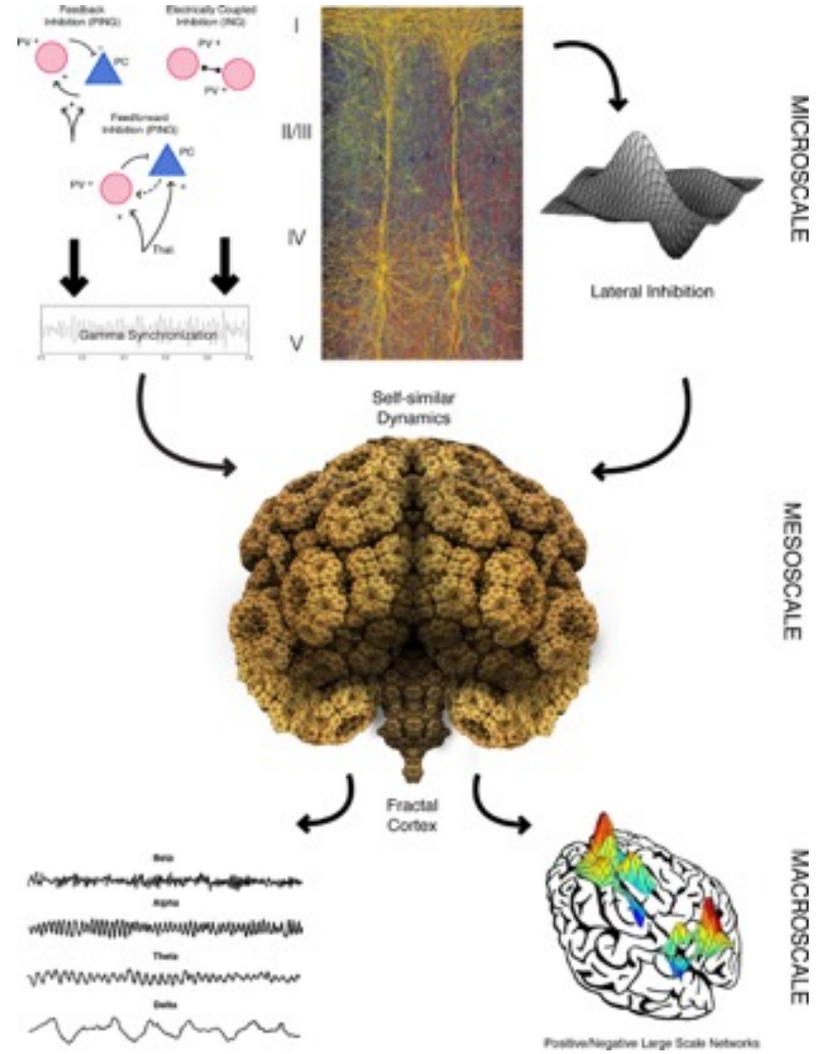
Hubs varieties



Looking at brain function from yet another complementary angle.
How to integrate

Nodes in brown overlap between PSS and network metrics.

The bottom of the barrel

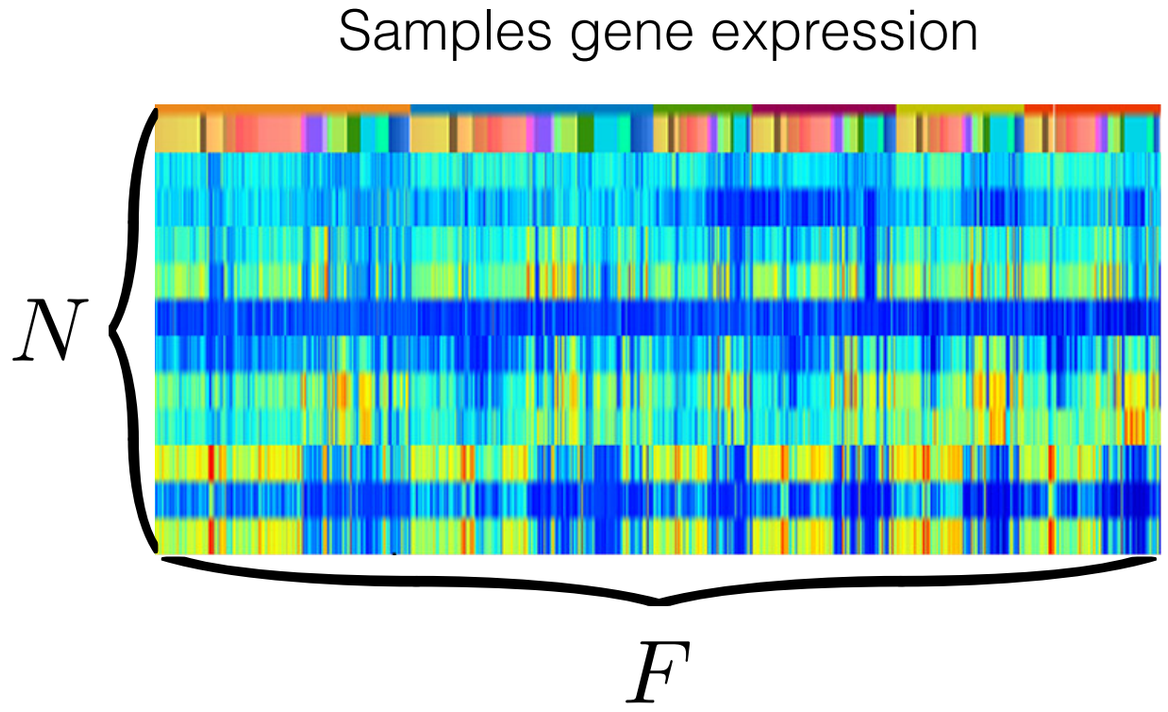


Gene expression

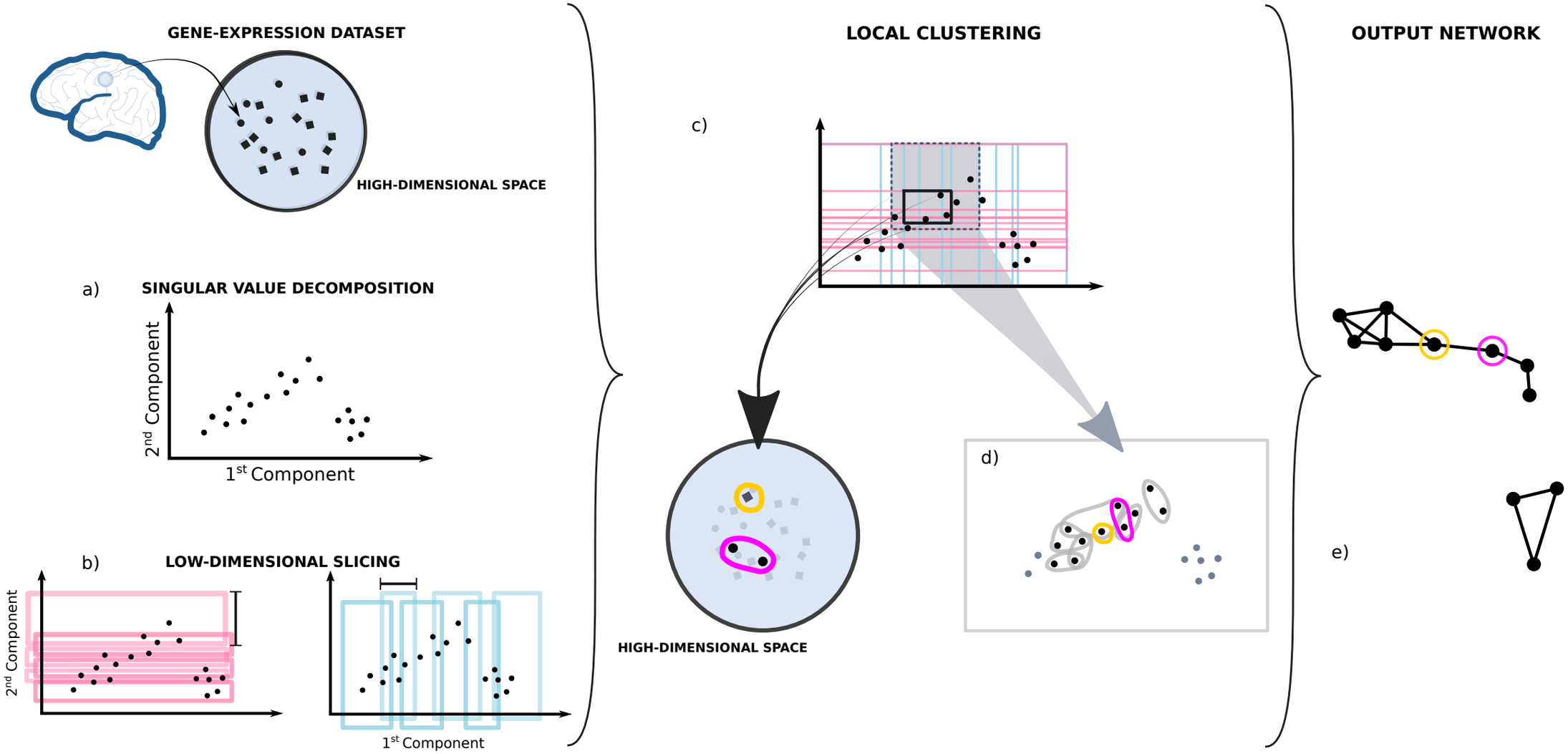
Ultimately, everything is shaped by gene expression.
Altered neuroschemistry only uses structure constrained by genes.

Allen Human Brain Atlas spatial gene expression patterns

The Allen Institute provides vast amount of freely available data. Including gene expression for samples taken in human brain http://portal.brain-map.org

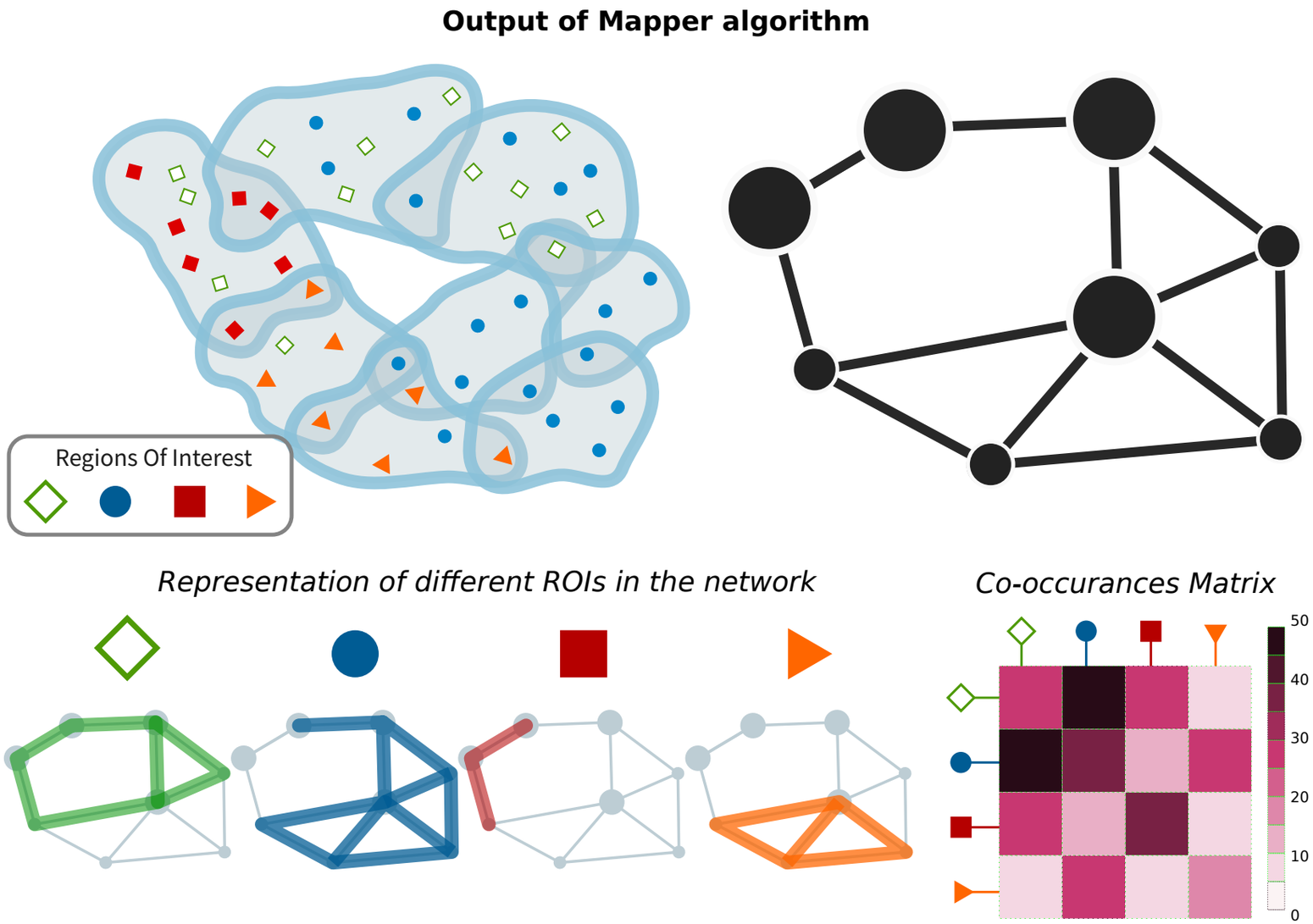


2D Mapper



Patania *et al.* Network Neuroscience (2019)

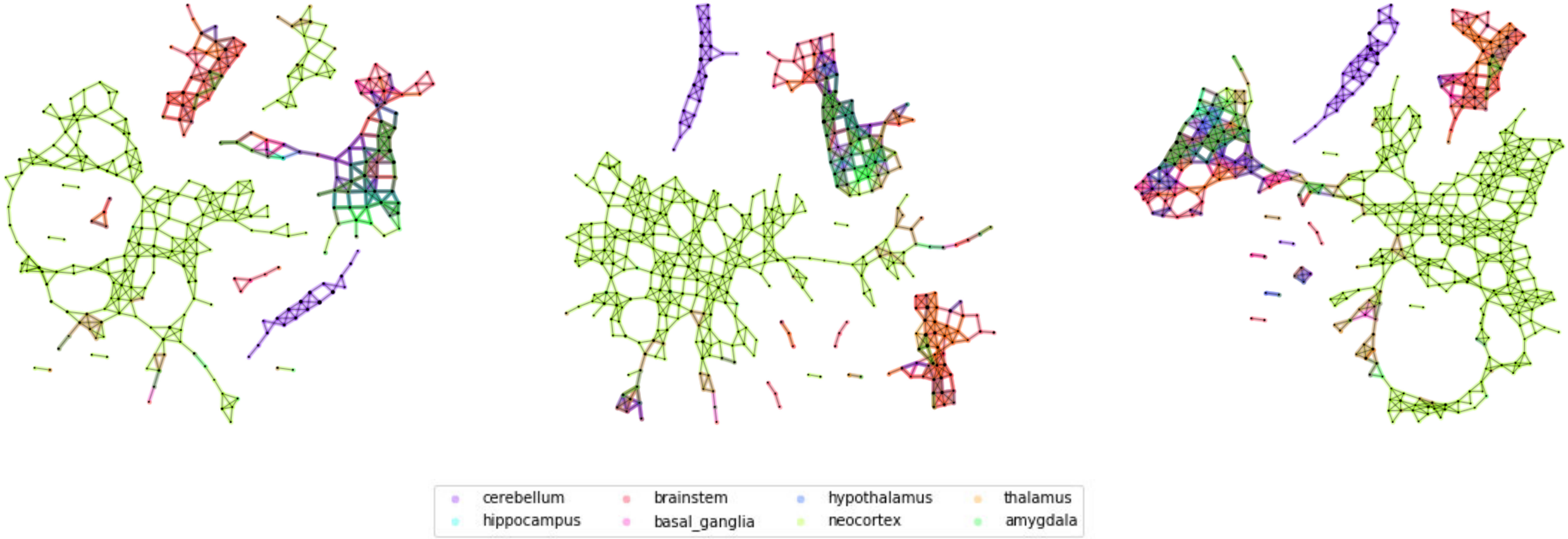
Spatial homogeneity



Using gene sample location metadata.

Patania *et al.* Network Neuroscience (2019)

Whole genome Mapper networks

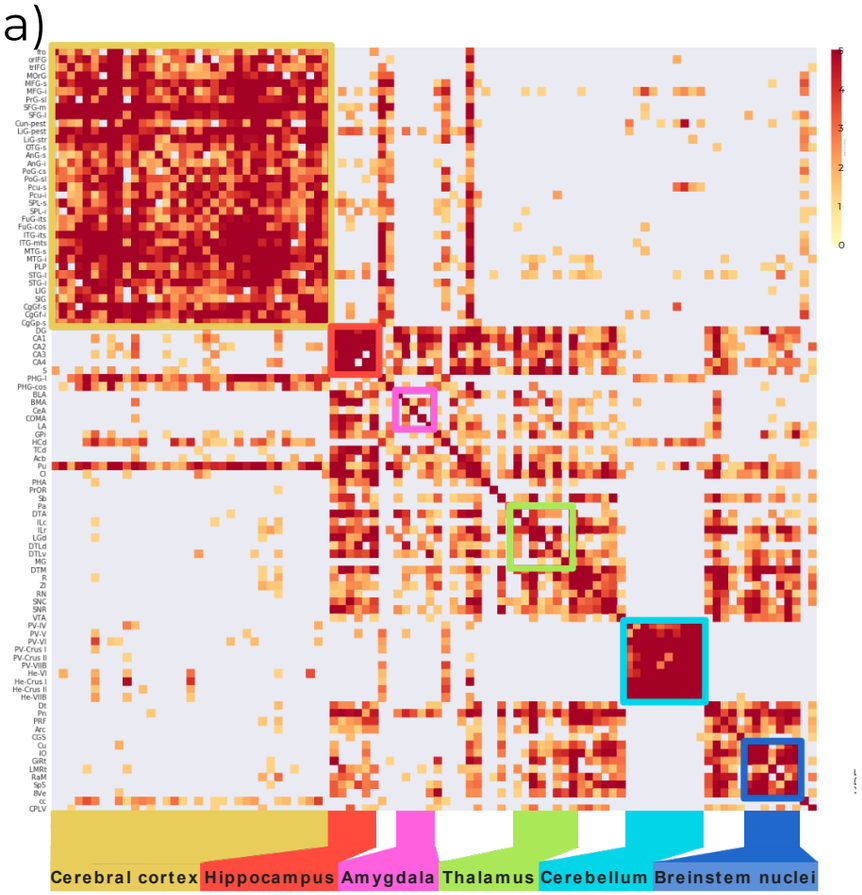


Networks obtained for different overlap values (25, 30, 35%).

Patania *et al.* Network Neuroscience (2019)

Validation

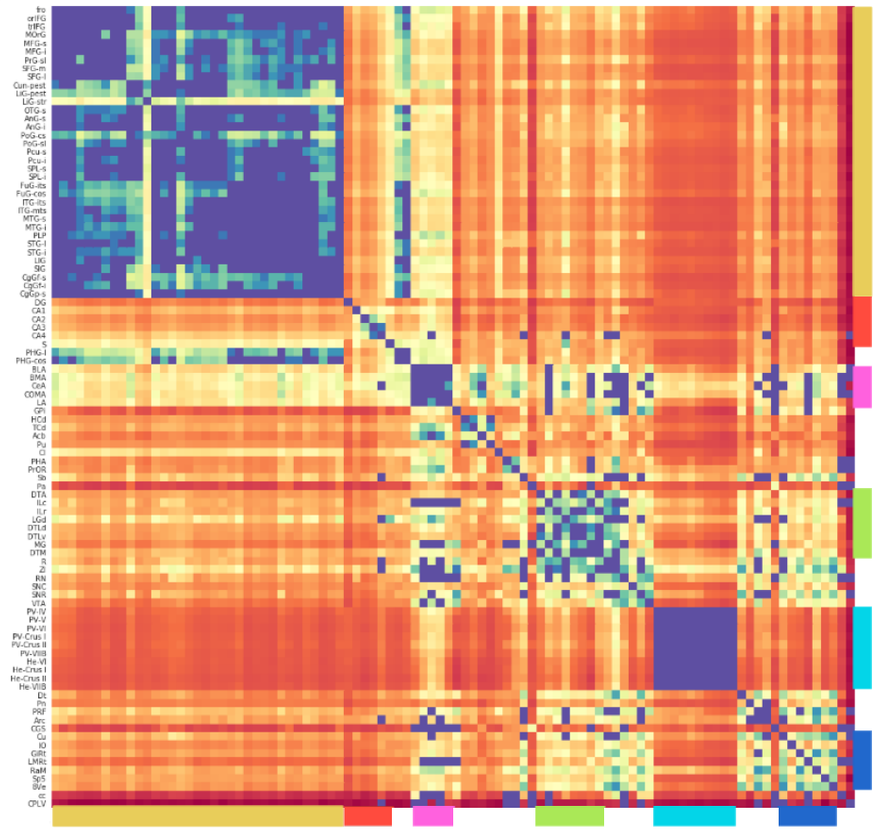
a)



Agreement matrix

Patania *et al.* Network Neuroscience (2019)

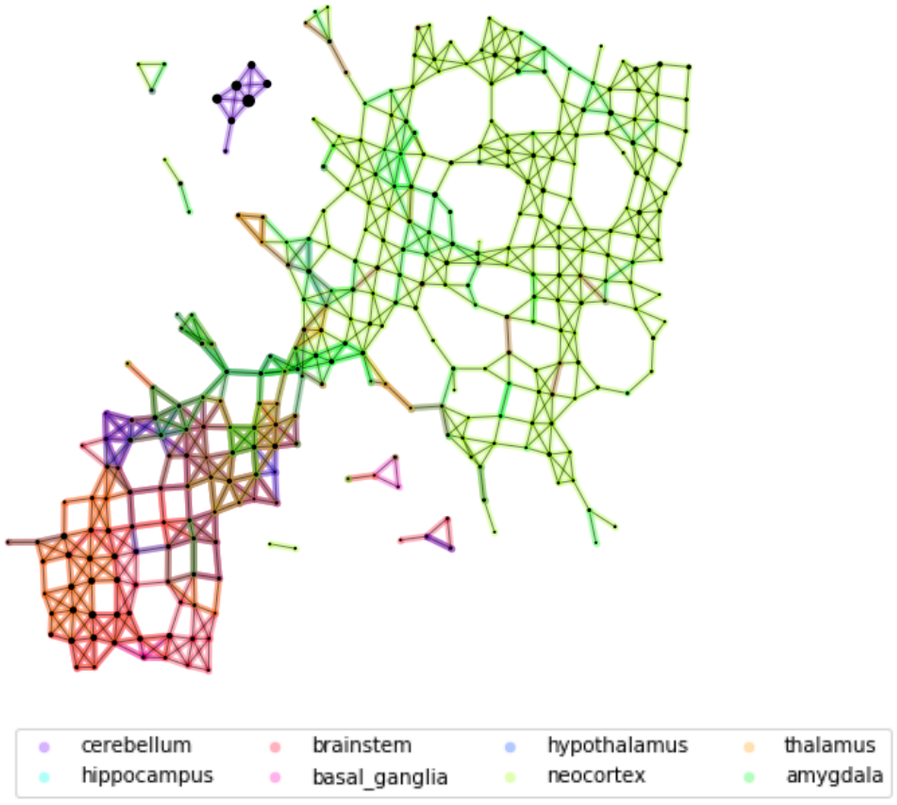
b)



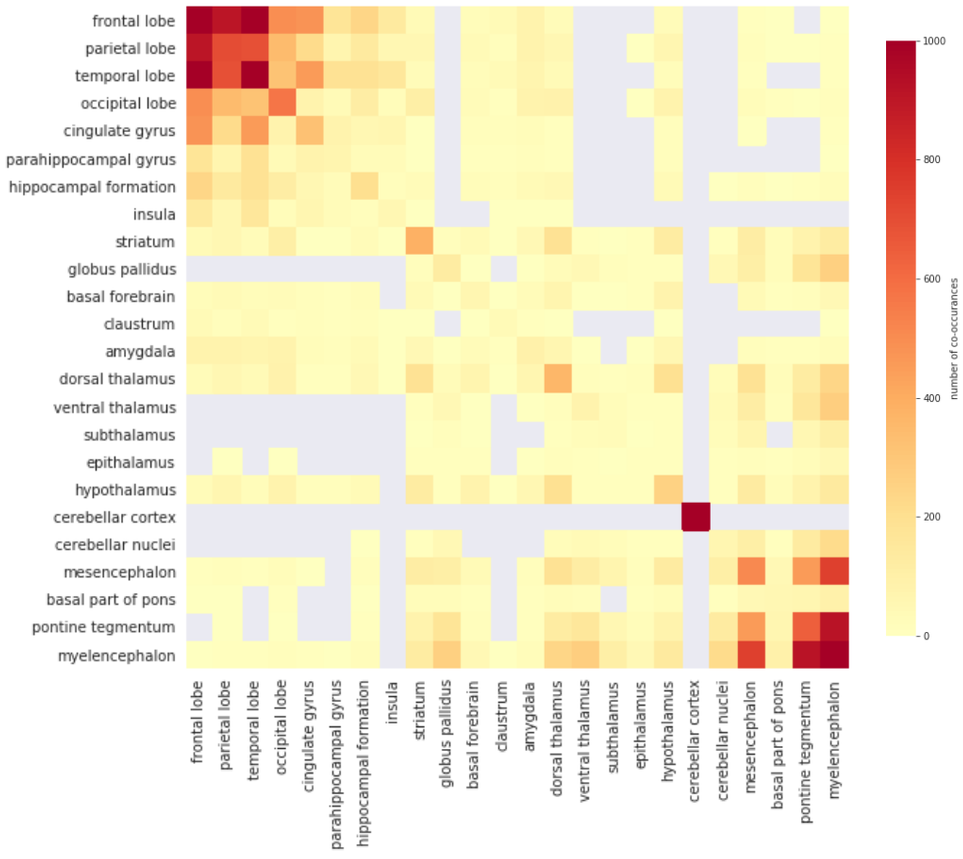
Co-expression matrix

Hawrylycz *et al.* Nature Neuroscience(2015).

The dopamine system (I)

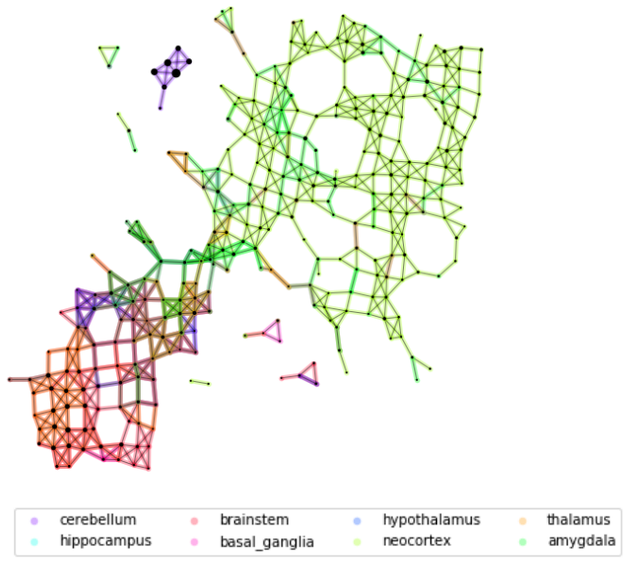


Dopamine Mapper network

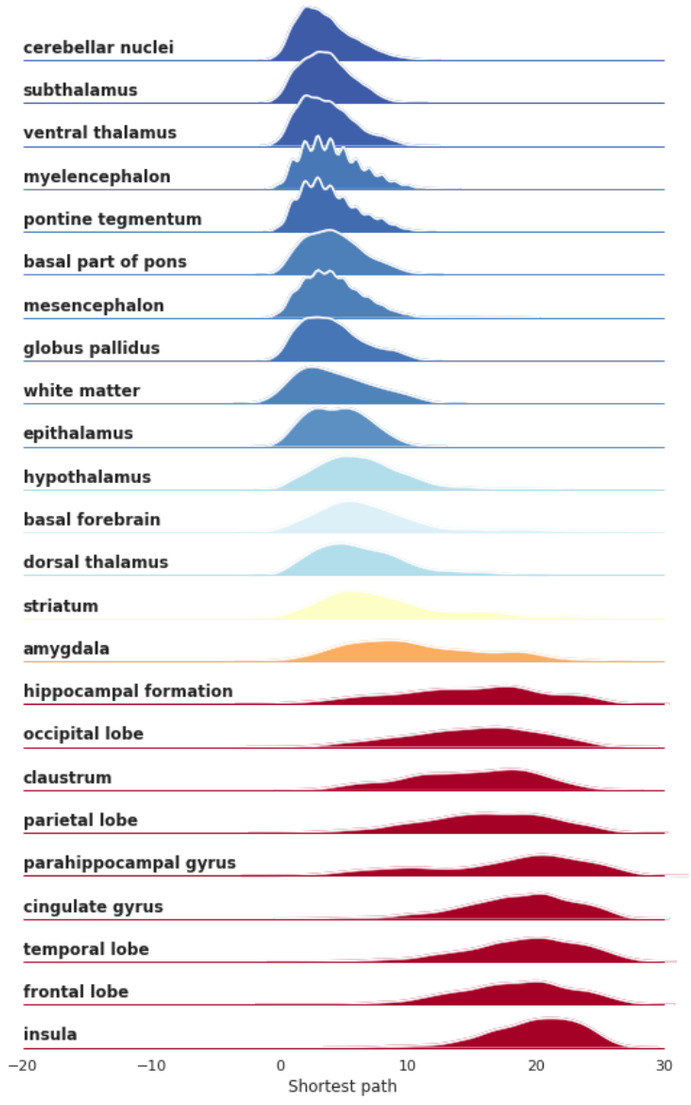


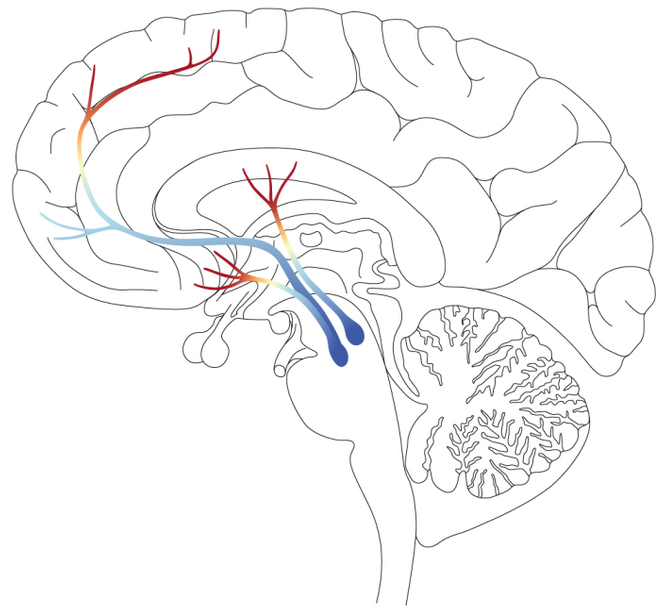
Agreement matrix

The dopamine system (II)



Dopamine Mapper network

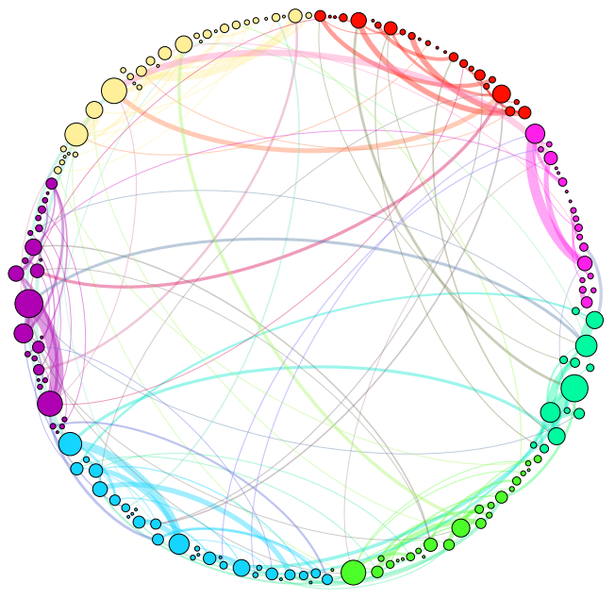


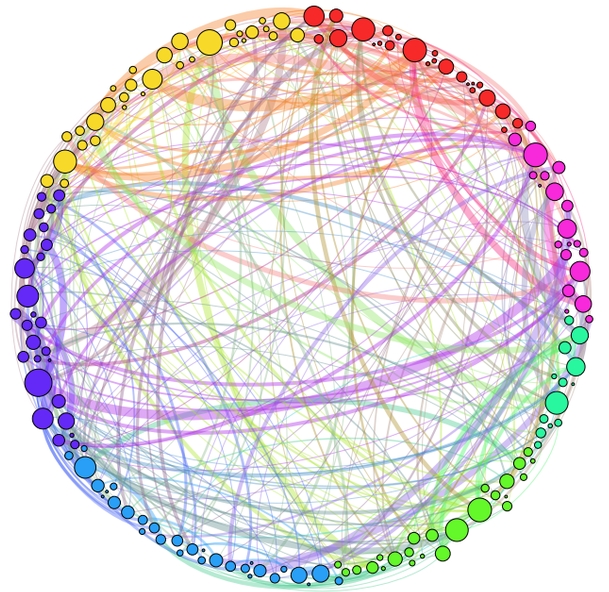


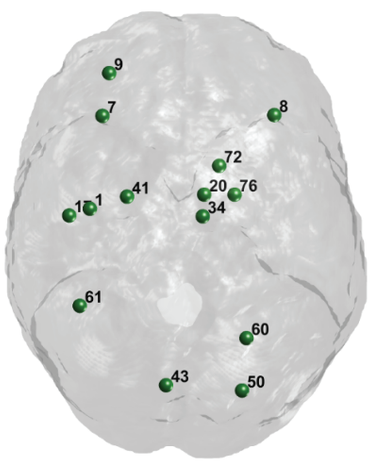
Dopamine pathway

Shortest paths from the substantial nigra

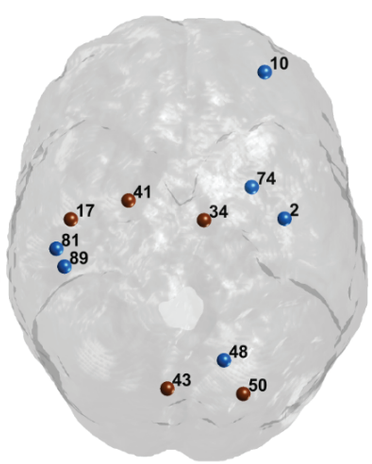
Integration in methods: meta-data, modalities and approach



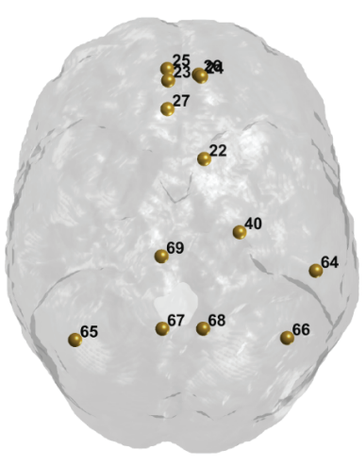




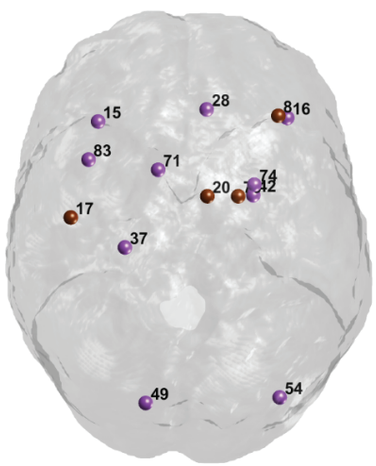
PSS



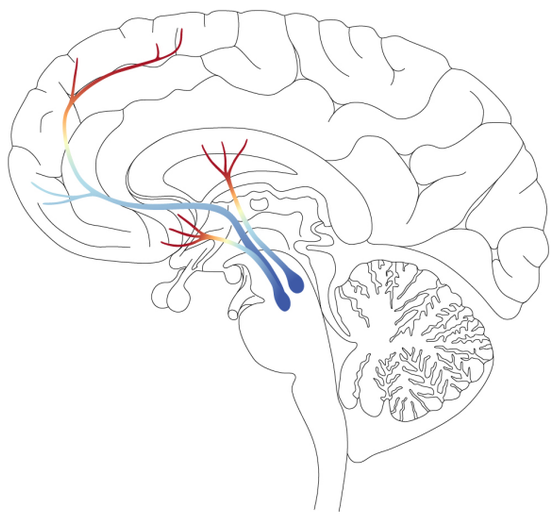
DC



Eff



BC



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Thank you for listening, questions?

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