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Characterizing Brain Structure-Function Relationship using Graph Diffusion Approaches

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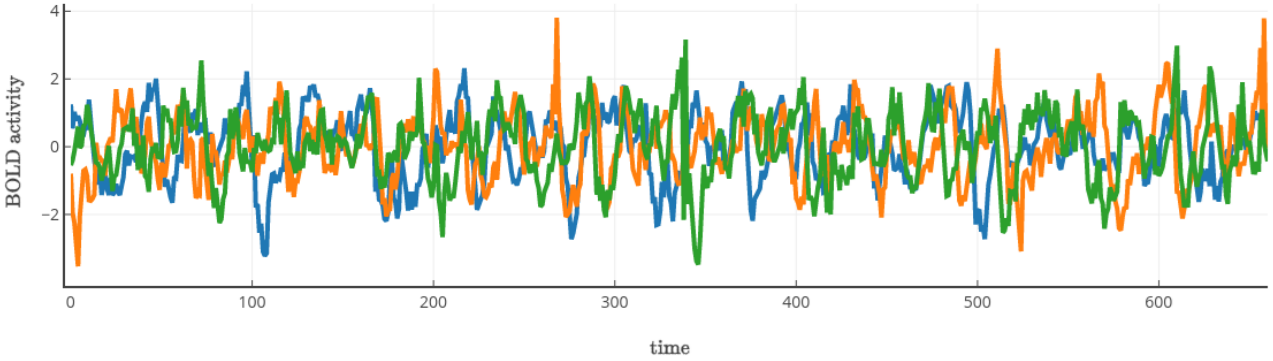
Brains, Dynamics and Computation: A Workshop in Network Neuroscience
Institute of Mathematical Sciences (IMSc), Chennai, May 22-June 4, 2025

Outline

- What are Structural Connectivity (SC) & Functional Connectivity (FC)?
- State the SC-FC problem
- Laplacian operator for graph
- Graph Diffusion
  - Single diffusion kernel (SDK) for predicting FC
  - Multiple Kernel Learning (MKL)
  - Graph Wavelet Diffusion – Every ROI can have its own diffusion scale
- Summary & Future Directions

Functional Magnetic Resonance Imaging (fMRI)

Brain activation patterns when engaged in tasks give insights about task-related activation



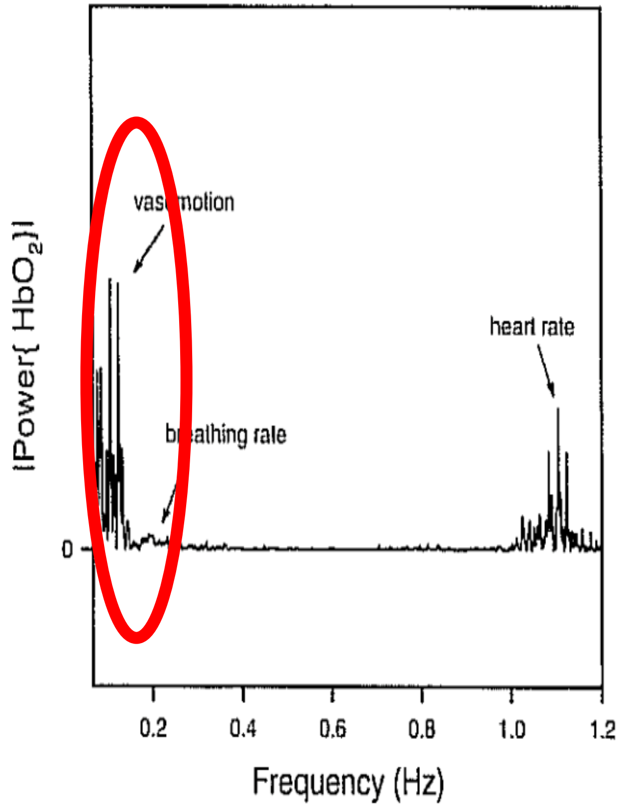
Exciting Discovery in the last two decades: Resting brain never rests!

What is (resting state) RS-fMRI?

The brain is always active (restless!), even in the absence of explicit input or output.

RS-fMRI focuses on spontaneous low frequency fluctuations (<0.1 Hz) in the BOLD signal.

Biswal et al. (1995) generated resting-state maps of motor cortex

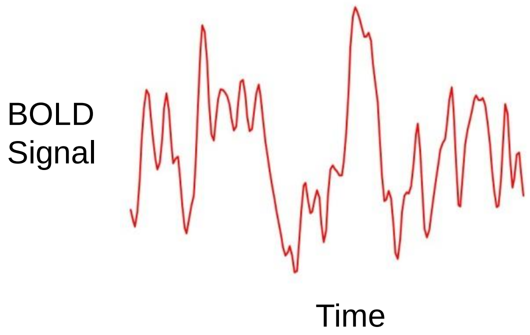


Elwell et al., 1999

RS-fMRI reveals the intrinsic functional connectivity of the brain

Functional Connectivity

r = 0.80



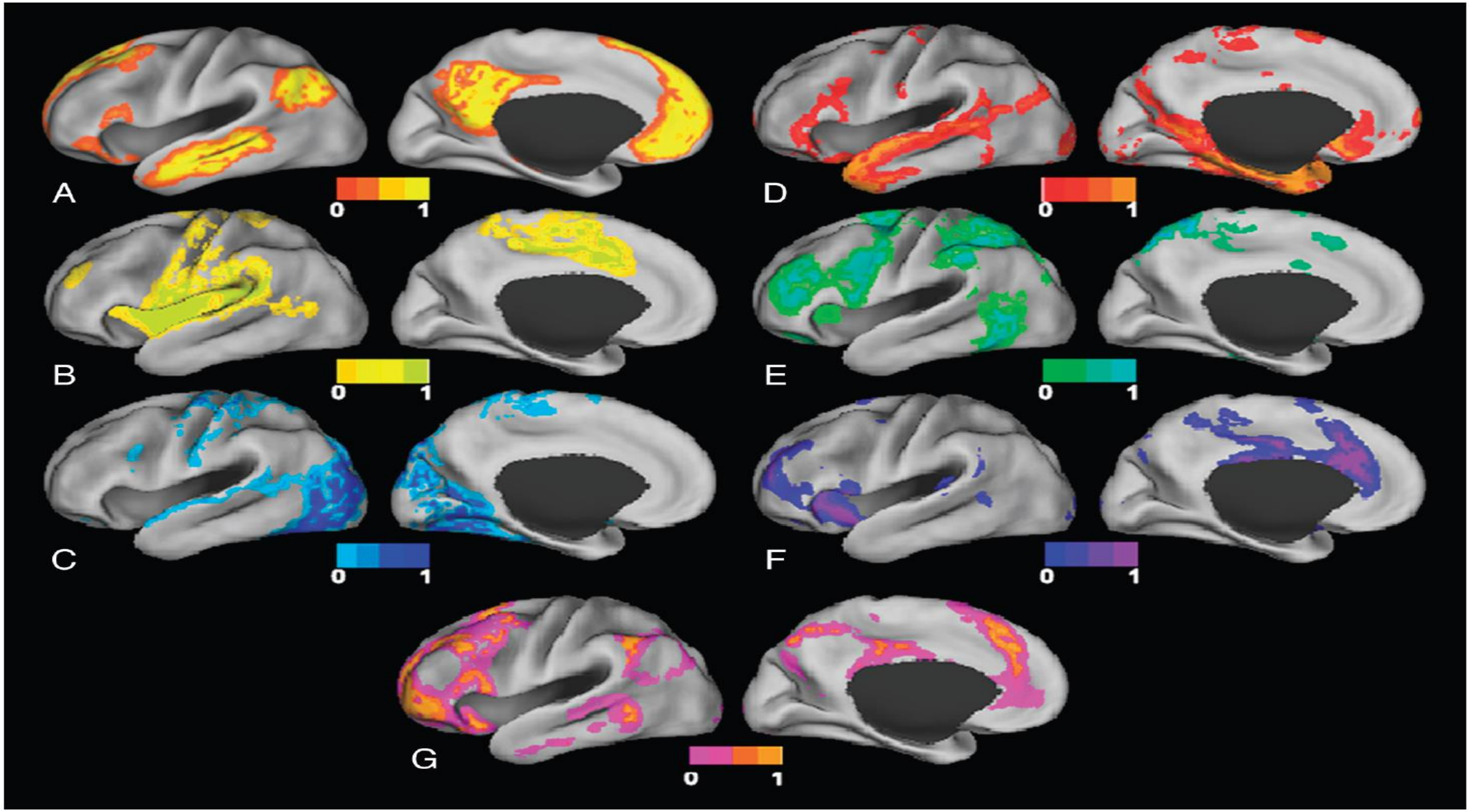
r = 0.59

r = 0.75

Seed-based Correlation Approach

Synchronous activations among regions that are spatially distinct, occurring in the absence of a task or stimulus correspond to Resting State Networks (RSN)

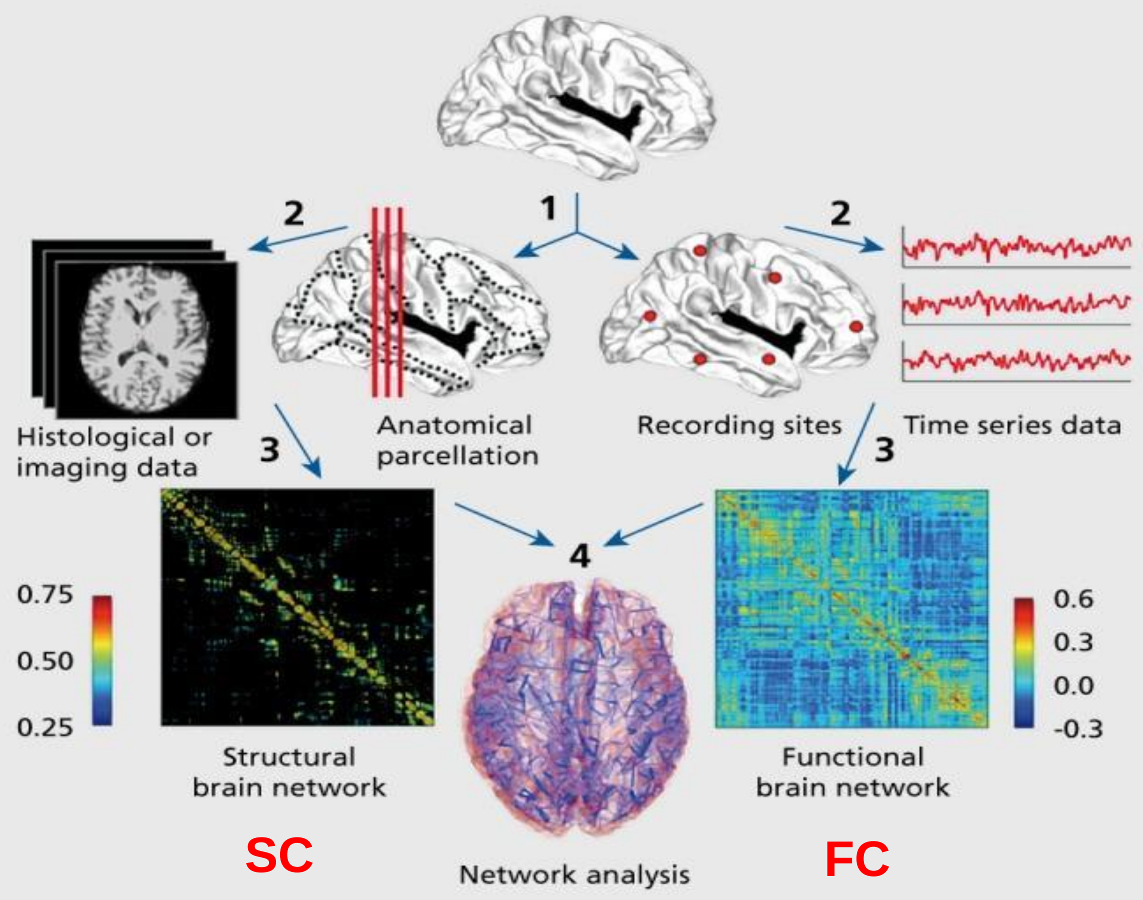
RSNs



Lee, et al., AJNR 2013

A, Default mode network. B, Somatomotor network. C, Visual network. D, Language network. E, Dorsal attention network. F, Ventral attention network. G, Frontoparietal control network

Structure-Function Relationship



Sporns *et al.* (2011)

Structural Connectivity (SC): Number or strength of white-matter fiber streamlines connecting each of the region-pairs.

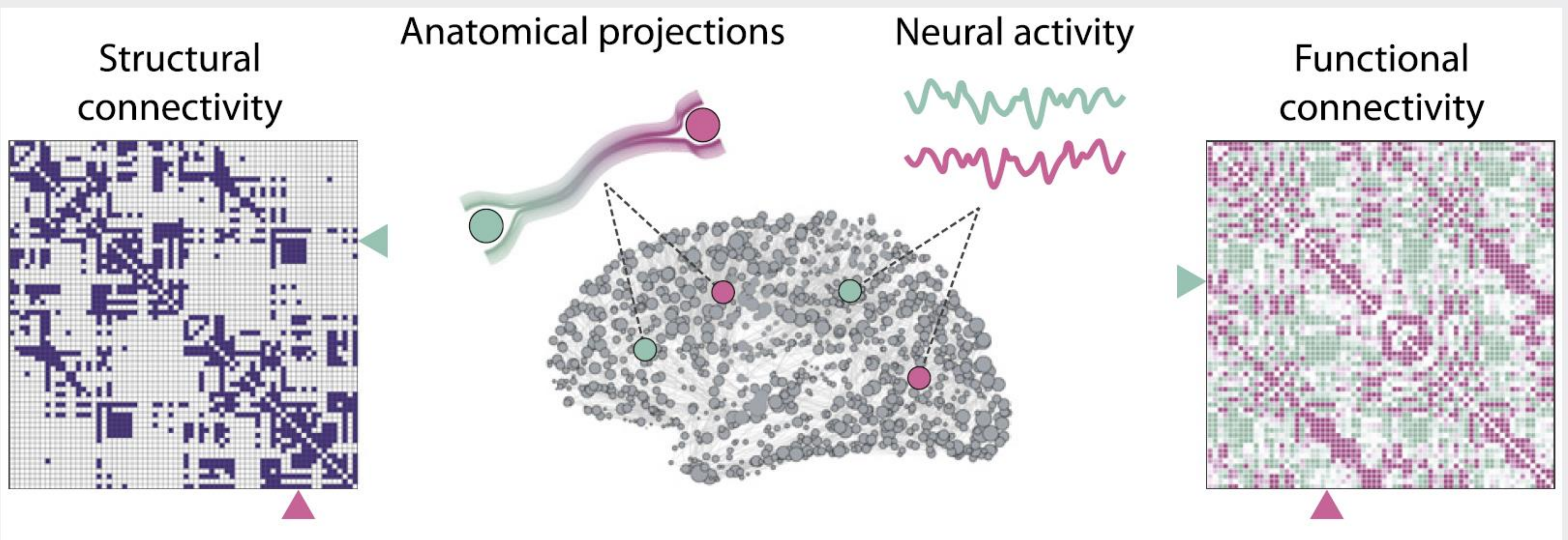
Functional Connectivity (FC): Pairwise statistical dependence between BOLD time-series of regions.

Holy grail!

Q: How does FC arise from SC?

Can we recover SC from FC?

Measuring the Connectivity



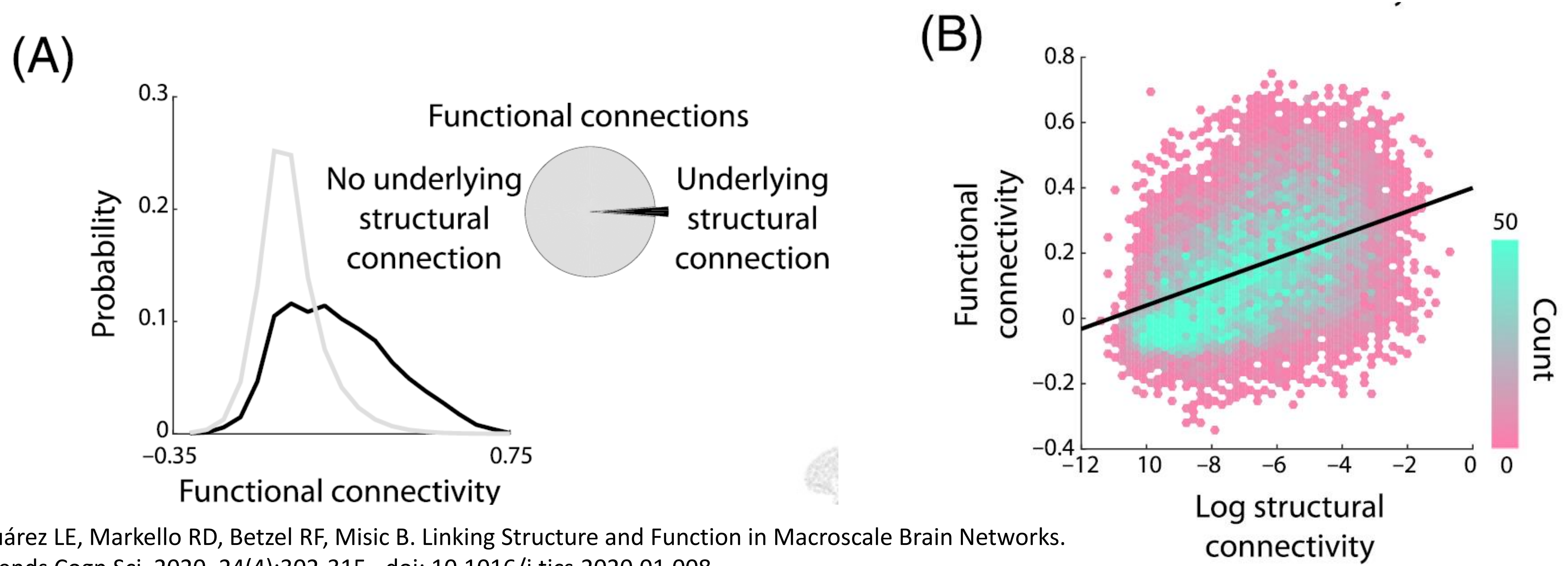
SC

FC

Suárez LE, Markello RD, Betzel RF, Misic B. Linking Structure and Function in Macroscale Brain Networks. Trends Cogn Sci. 2020, 24(4):302-315.

Imperfect SC-FC Correspondence

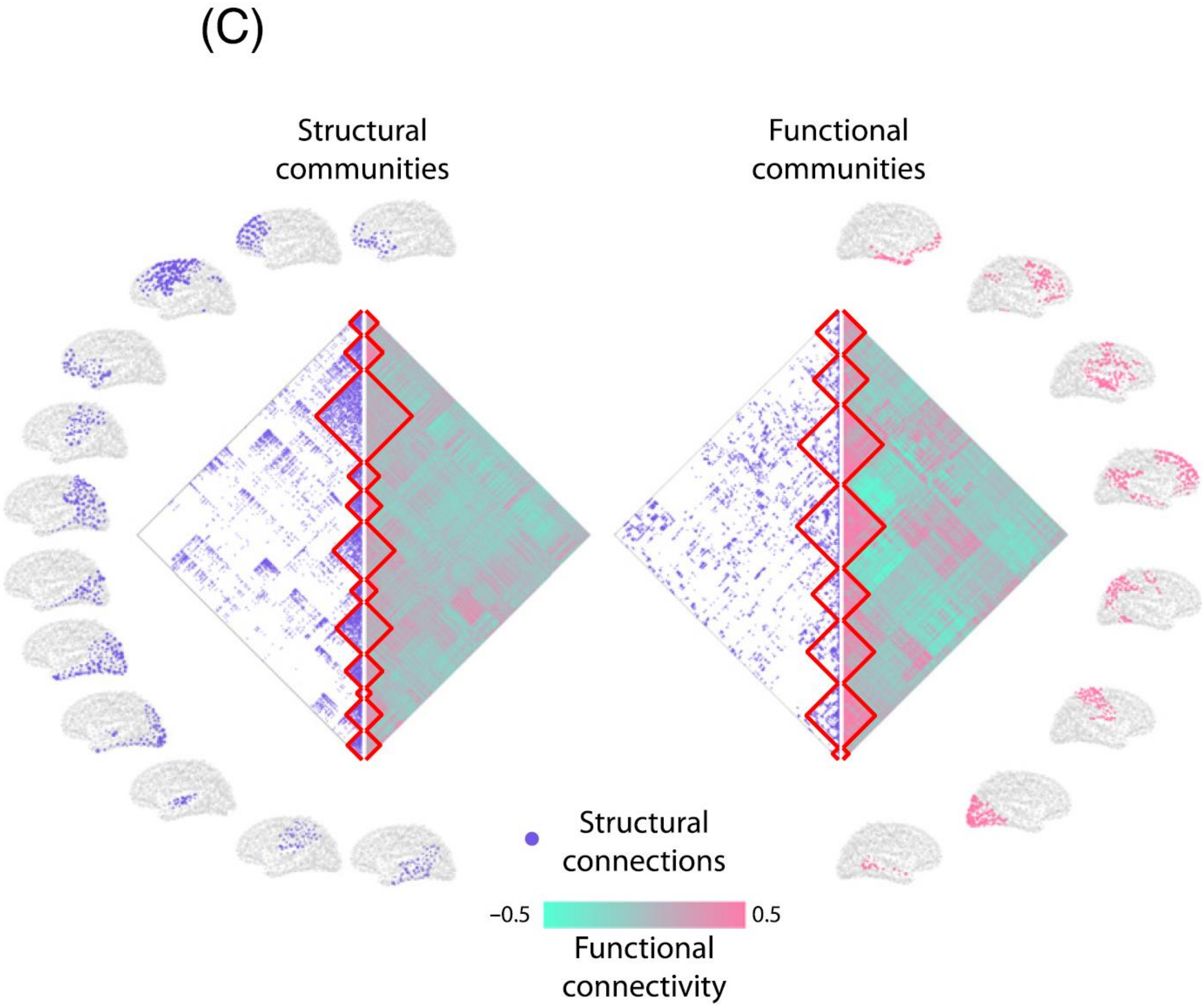
- The persistent and reproducible nature of brain activity during rest makes resting-state FC an ideal starting point to study structure–function relationships. But the correspondence between SC-FC is imperfect.



Suárez LE, Markello RD, Betzel RF, Misic B. Linking Structure and Function in Macroscale Brain Networks. Trends Cogn Sci. 2020, 24(4):302-315. doi: 10.1016/j.tics.2020.01.008

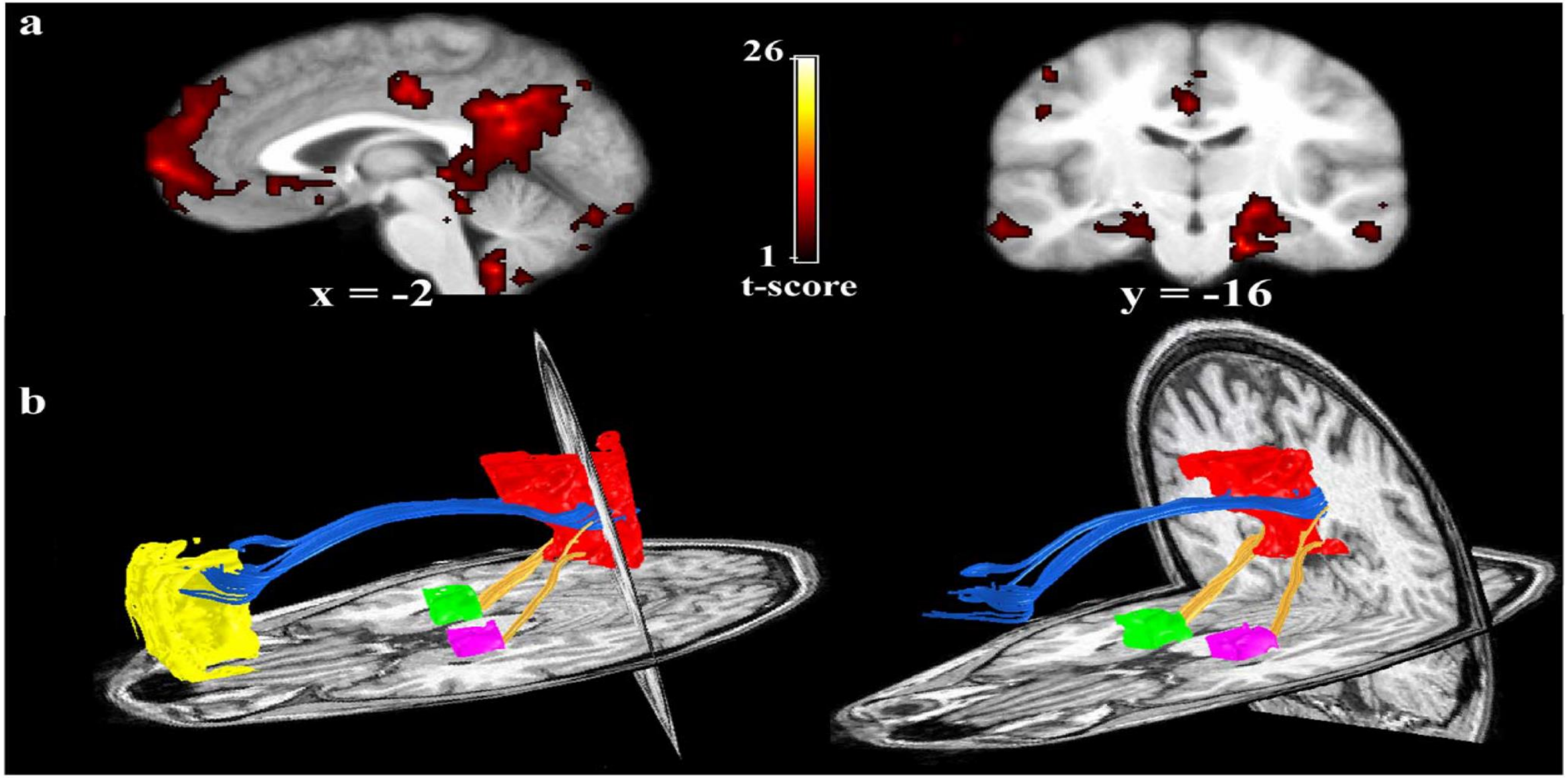
Imperfect SC-FC

- Structure and function diverge at the mesoscopic scale.
- Community detection for structural and functional networks yields different solutions
  - RSNs tend to encompass spatially distributed systems with perceptual, cognitive, and affective relevance
  - Structural networks tend to be more spatially constrained.



Functional Connectivity (FC) versus Structural Connectivity (SC)

Lee, et al., AJNR 2013



DMN is an example where SC-FC mapping is not direct!

Discordance between SC and FC

- Communities or modules recovered from structural networks are assortative.
  - Thus, Clustering or community detection methods typically fail to identify a default mode-like structural network, because not all parts of the network are anatomically inter-connected.
- Structural connections (anatomical wiring) is subject to material, spatial, and metabolic constraints.
- Communities recovered from functional networks are disassortative.
  - Functional interactions are much less distance-dependent
  - Propensity of two regional time courses to correlate is driven not only by direct signaling between them, but also by the common inputs they receive from sensory organs and from the entire network.

Need for incorporating Higher-order Interactions!

Derivation of Laplacian Operator

The Laplacian operator is defined as:

$$\Delta = \frac{\partial^2}{\partial x^2}$$

acting on functions $f(x)$, with analogous forms in other dimensions.

Let $f(x)$ be a function and suppose we aim to approximate the second derivative $\frac{d^2 f}{dx^2}(x)$. We can use a centered difference approximation as follows:

$$\frac{d^2 f}{dx^2} \approx \frac{f'(x + \frac{\Delta x}{2}) - f'(x - \frac{\Delta x}{2})}{\Delta x}$$

$$= \frac{1}{\Delta x}\left[\frac{f(x+\Delta x) - f(x)}{\Delta x} - \frac{f(x) - f(x - \Delta x)}{\Delta x}\right]$$

$$= \frac{1}{(\Delta x)^2}\left[f(x+\Delta x) - f(x) + f(x - \Delta x) - f(x)\right]$$

$$= \frac{1}{(\Delta x)^2}\left[f(x+\Delta x) + f(x - \Delta x) - 2f(x)\right].$$

Note that if we take $\Delta x = 1$, this approximation depends only on the function values at the integer points.

Derivation of Laplacian Operator

Now, consider the graph consisting of vertices on the integers of the real line, with edges connecting consecutive integers. For any function f defined on the vertices, the Laplacian can be computed as:

$$\Delta f(v_i) = f(v_{i+1}) + f(v_{i-1}) - 2f(v_i)$$

for any vertex v_i. The Laplacian is represented as an infinite matrix of the form:

$$\Delta f = \begin{bmatrix} \ddots & \ddots & \ddots & & \\ & 1 & -2 & 1 & 0 \\ & 0 & 1 & -2 & 1 \\ & & \ddots & \ddots & \ddots \end{bmatrix} \begin{bmatrix} \vdots \\ f(v_{i-1}) \\ f(v_i) \\ f(v_{i+1}) \\ \vdots \end{bmatrix}.$$

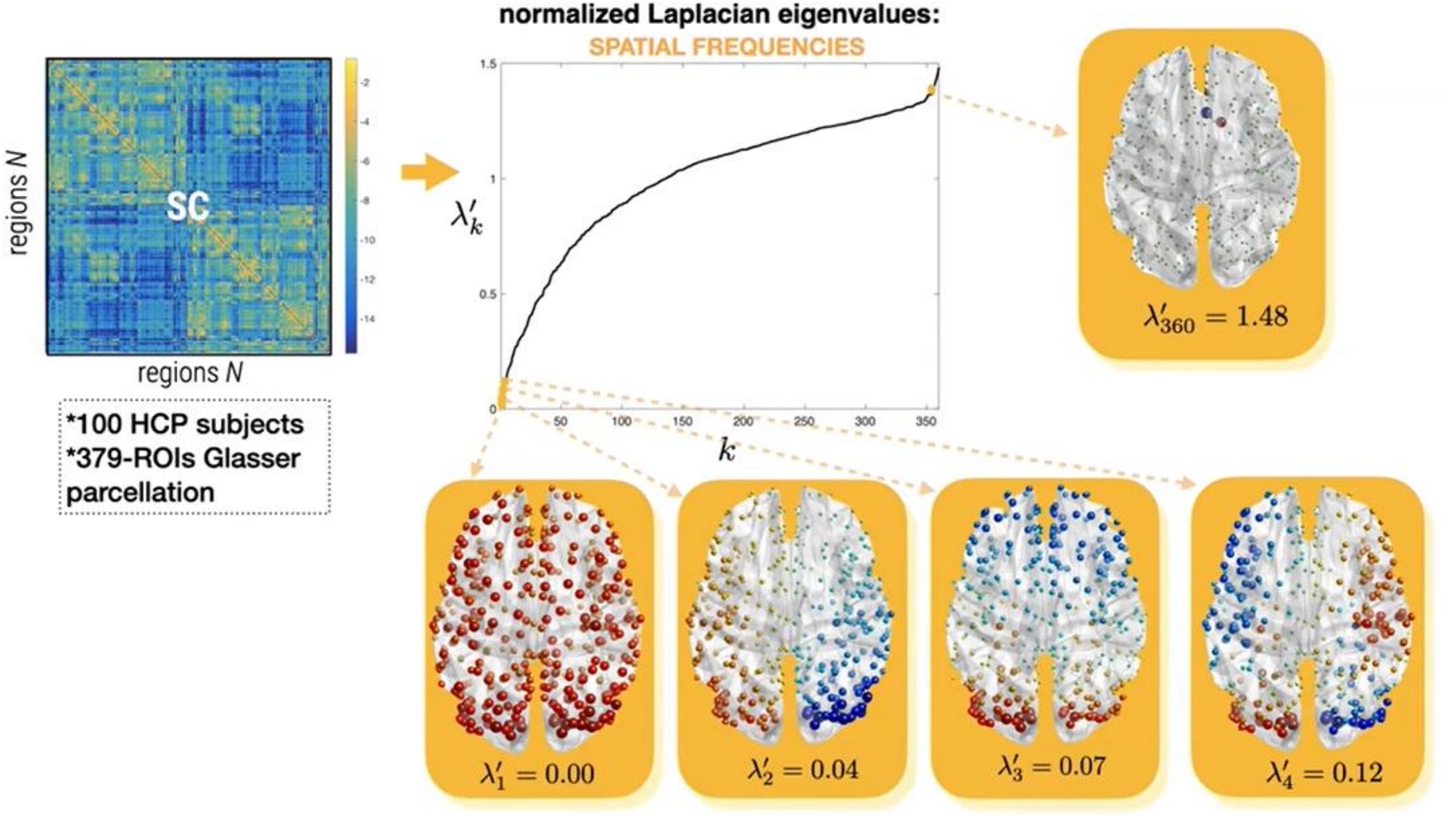
It is also important to note that this matrix is equivalent to the adjacency matrix minus twice the identity matrix. The number 2 represents the degree of each vertex, so we can express the Laplacian matrix as:

$$L = A - D,$$

where A is the adjacency matrix, and D is the diagonal matrix containing the degrees (also known as the degree matrix).

Structural Harmonics

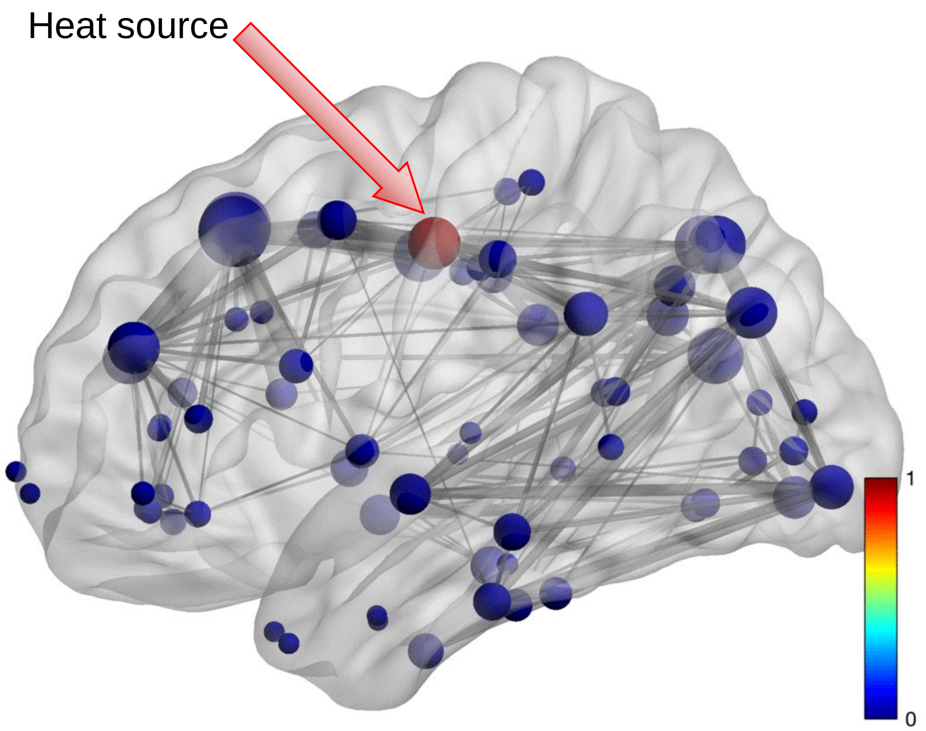
- Spectral Graph Theory
- $L = UVU^T$
- $U \rightarrow Eigenvector$
- $V \rightarrow Eigenvalue$



1. Pang, James C., et al. "Geometric constraints on human brain function." *Nature* 618.7965 (2023): 566-574.
2. Preti, M.G., Van De Ville, D., 2019. Decoupling of brain function from structure reveals regional behavioral specialization in humans. Nat. Commun. 10, 4747. doi:10.1038/s41467-019-12765-7.

Graph Diffusion

- Laplacian Heat Diffusion: $\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2}$
- Discretize space derivate for graph data: $L = A - D$
  - $\frac{\partial u}{\partial t} = Lu$
  - $u(t) = e^{(-Ls)}u$
  - $e^{(-Ls)}$ is the heat kernel operator, where s represents scale.



Network Diffusion Model

- Consider single region.
  - Region 1: $x_1(t)$
  - $\frac{dx_1}{dt} = -\beta x_1(t)$
- Pair of regions.
  - $\frac{dx_1(t)}{dt} = \beta \left(S_{1,2} \frac{1}{\delta_2} x_2(t) - x_1(t) \right)$
- N regions.
  - $\frac{dx_i(t)}{dt} = \beta \left(\sum_j S_{i,j} \frac{1}{\delta_j} x_j(t) - x_i(t) \right)$

Abdelnour, Farras, Henning U. Voss, and Ashish Raj. "Network diffusion accurately models the relationship between structural and functional brain connectivity networks." Neuroimage 90 (2014): 335-347.

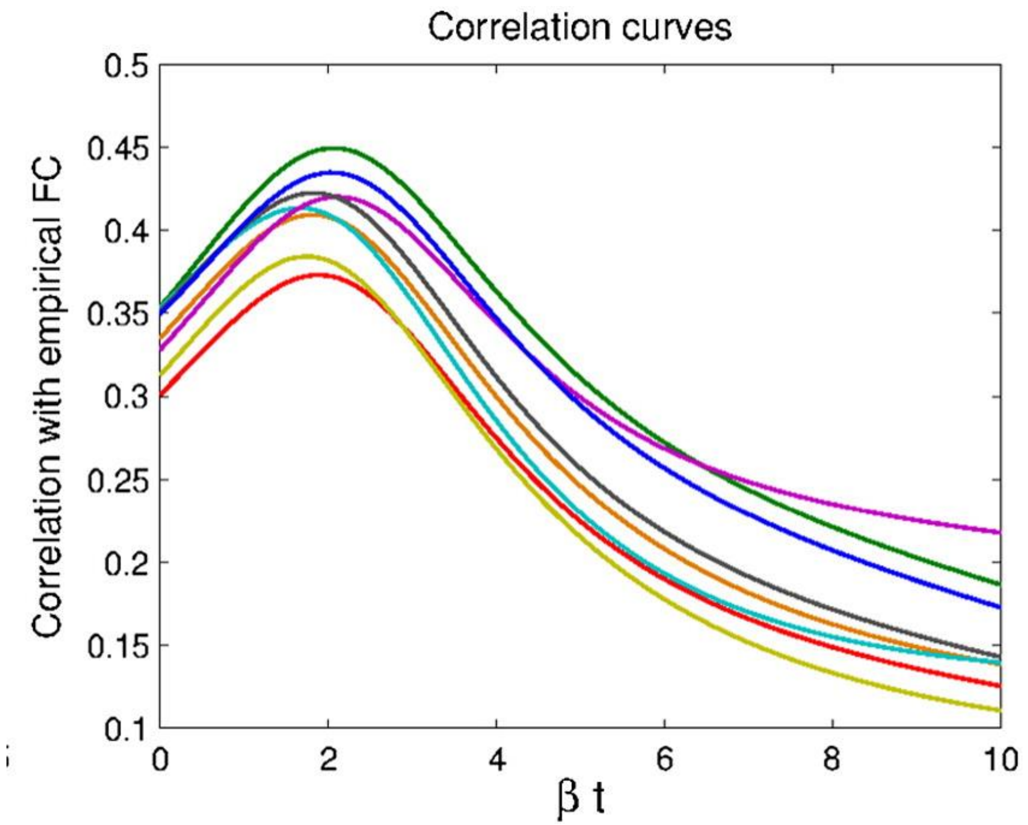
Network Diffusion Model

- $\frac{dx_i(t)}{dt} = \sum_{j=1}^{N} S_{i,j} x_j(t) - x_i(t)$ \\ Network Diffusion[1]
- $\frac{d\boldsymbol{x}(t)}{dt} = -L\boldsymbol{x}(t)$ \\ Concatenated for all i_s
- $\boldsymbol{x}(t) = e^{-Ls}\boldsymbol{x}(0)$

Single Diffusion Kernel (SDK) model

1. Abdelnour, Farras, Henning U. Voss, and Ashish Raj. "Network diffusion accurately models the relationship between structural and functional brain connectivity networks." Neuroimage 90 (2014): 335-347.

SDK: Results



- Scales decided manually
- Physiological Meaning of the Scales not explained

Abdelnour, Farras, Henning U. Voss, and Ashish Raj. "Network diffusion accurately models the relationship between structural and functional brain connectivity networks.“ Neuroimage 90 (2014): 335-347.

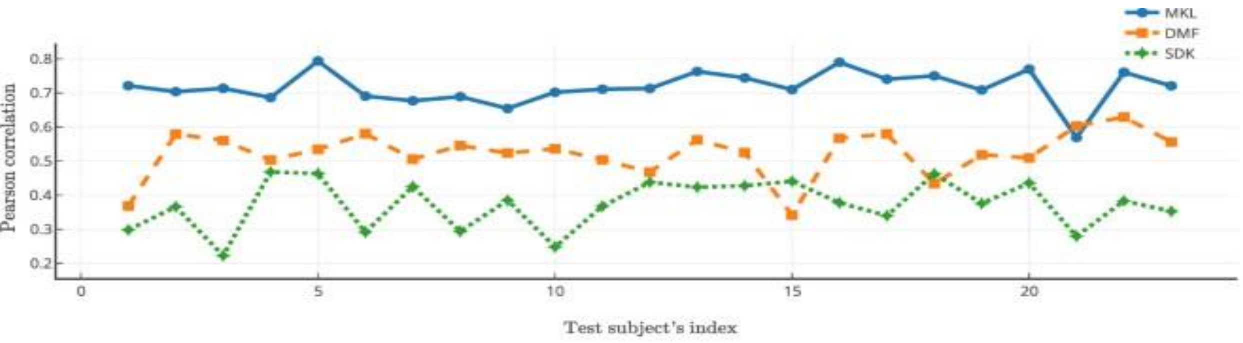
Multiple Kernel Learning (MKL)

- Hypothesis: FC is combination of diffusion kernels at different scales.
- $FC = \sum_{i=1}^{m} \pi_i \, e^{-Ls_i}$
- π_i are learned coefficients

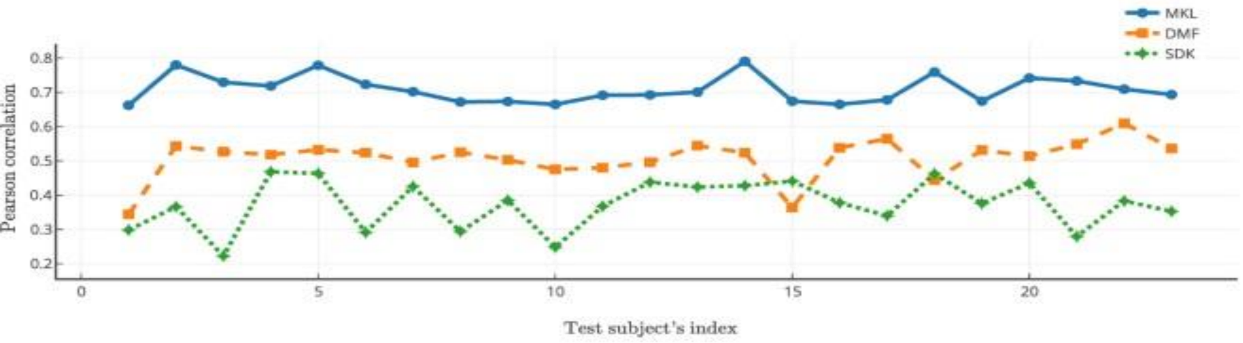
Laplacian of SC → Diffusion Kernels= H = e^{-sL} for multiple s values. → FC = $\Sigma \pi_i H_i$. Find π_i using Lasso regression.

Surampudi, S.G., Naik, S., Surampudi, R.B. et al. Multiple Kernel Learning Model for Relating Structural and Functional Connectivity in the Brain. Sci Rep 8, 3265 (2018).

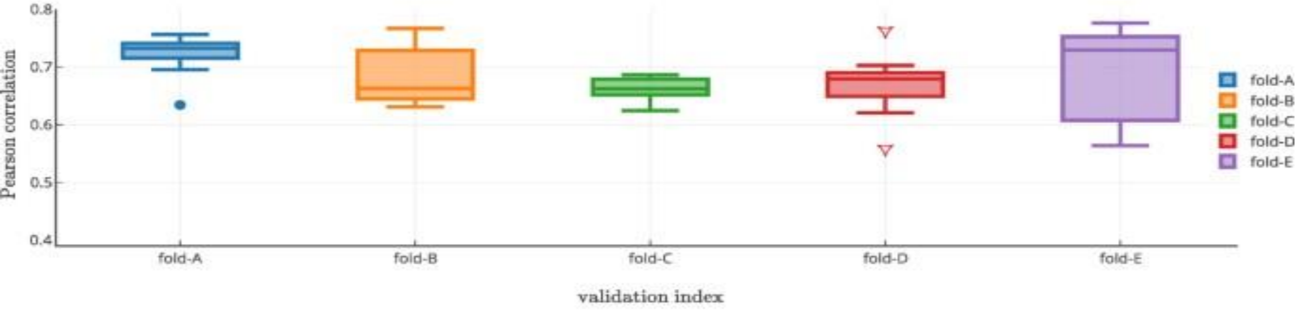
MKL -Results



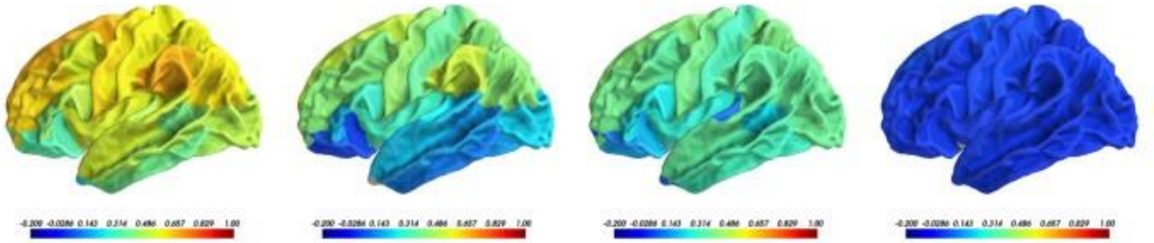
(a) Performance of models.



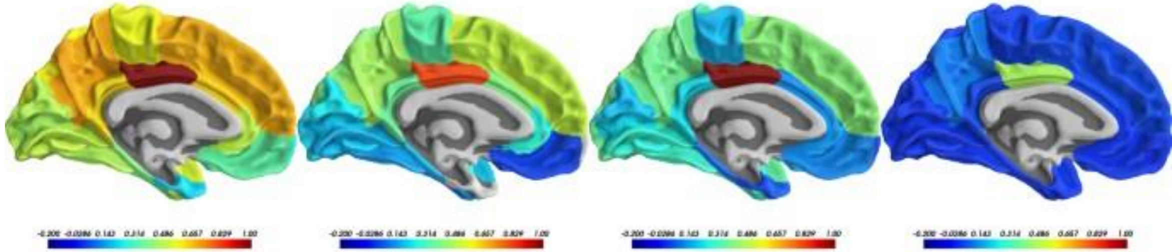
(b) Leave-one-out validation.



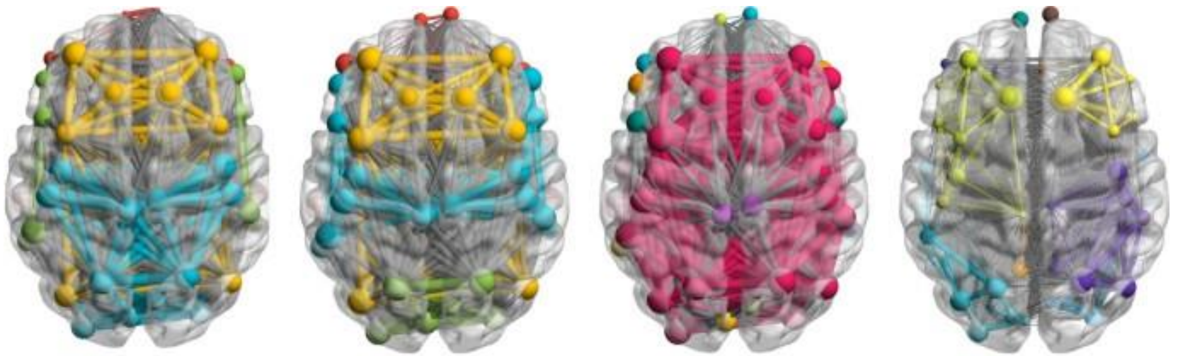
(c) 5-fold cross-validation



(a) Emp **(b)** MKL **(c)** DMF **(d)** SDK



(e) Emp **(f)** 0.71 **(g)** 0.52 **(h)** 0.37



(a) Emp **(b)** MKL **(c)** DMF **(d)** SDK

Wavelet Diffusion

- Wavelet Localization: $x_i = UG(s_i)U^T\delta_i$ \\ Wavelet Diffusion
- Asymmetric diffusion kernel: $\mathrm{K} = ||_i x_i$
- FC = LinearLayer($\mathrm{K}||\mathrm{S}$)

$s_1 < s_2 < s_3$

Jain, Chirag, Sravanthi Upadrasta Naga Sita, Avinash Sharma, and Bapi Raju Surampudi. "Diffusion wavelets on connectome: Localizing the sources of diffusion mediating structure-function mapping using graph diffusion wavelets." *Network Neuroscience* (2025): 1-21.

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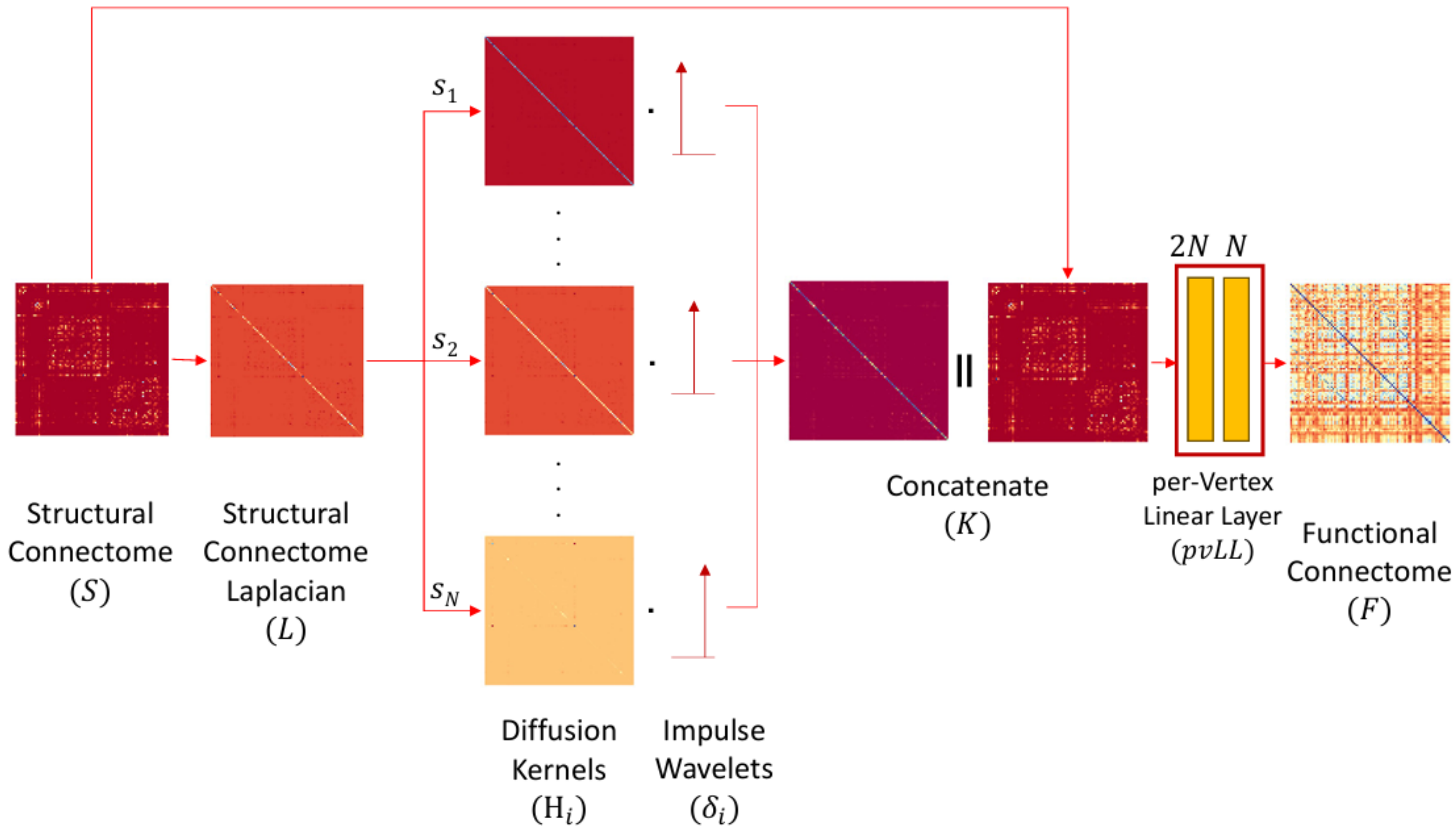

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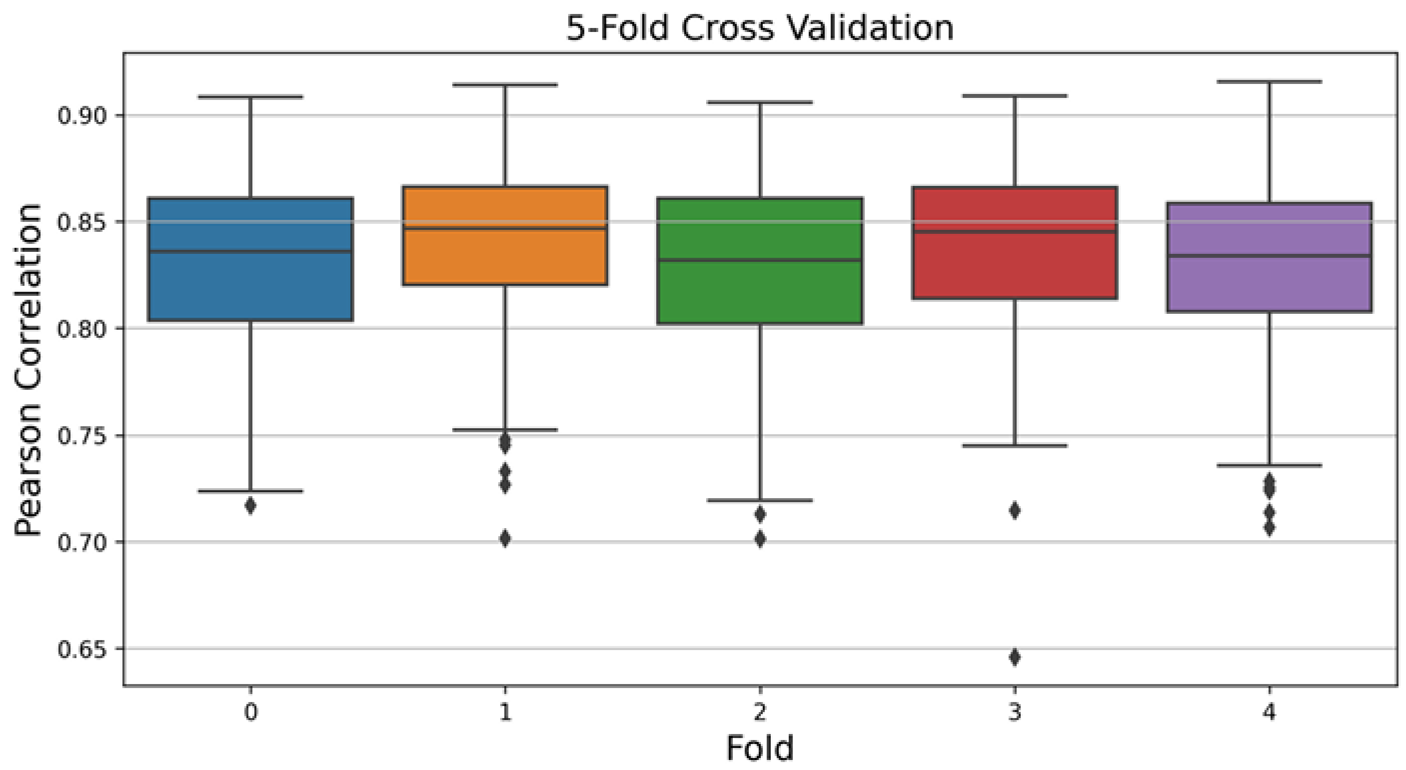
Results

- 5-fold CV
- Vary k & hidden layer size



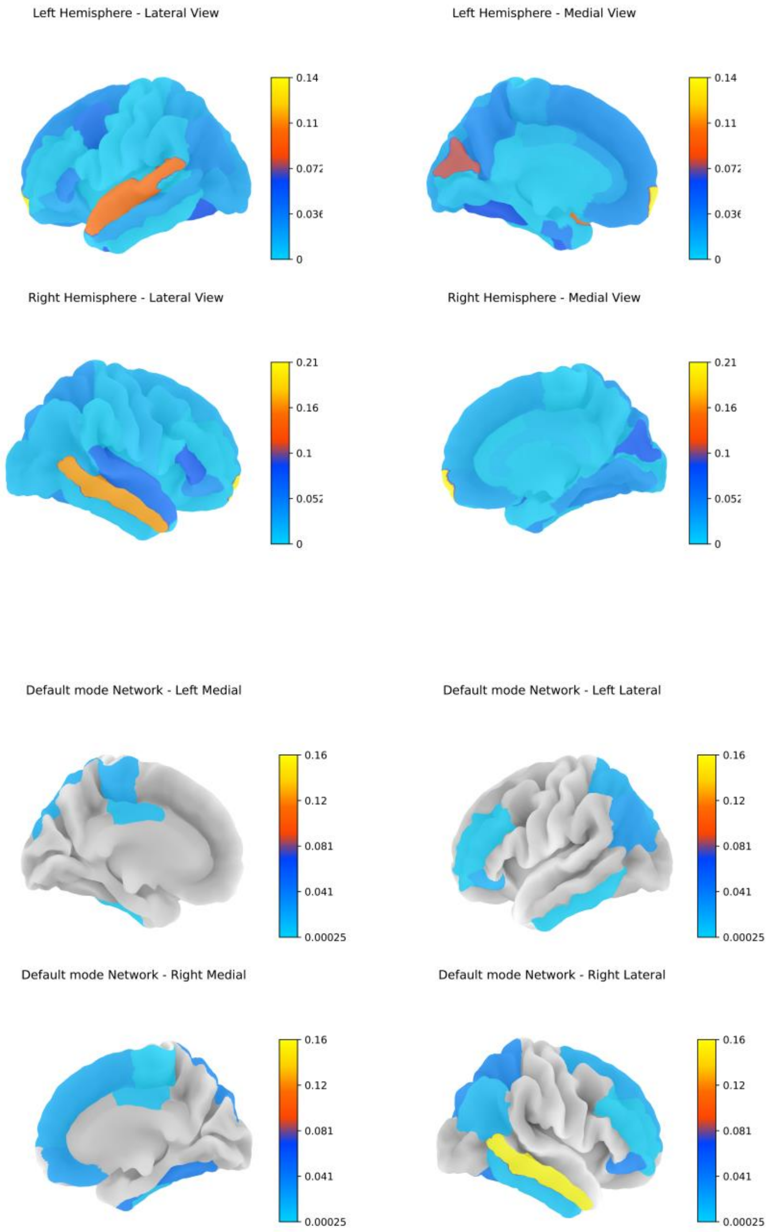
Model	Correlation
A-GHN (Oota et al., 2024)	0.788
MKL (Surampudi et al., 2018)	0.645
GNN (GCN + GTN) (Ji et al., 2021)	0.715
GCN Encoder Decoder (Li et al., 2019)	0.732
Graph Wavelet Diffusion	0.833

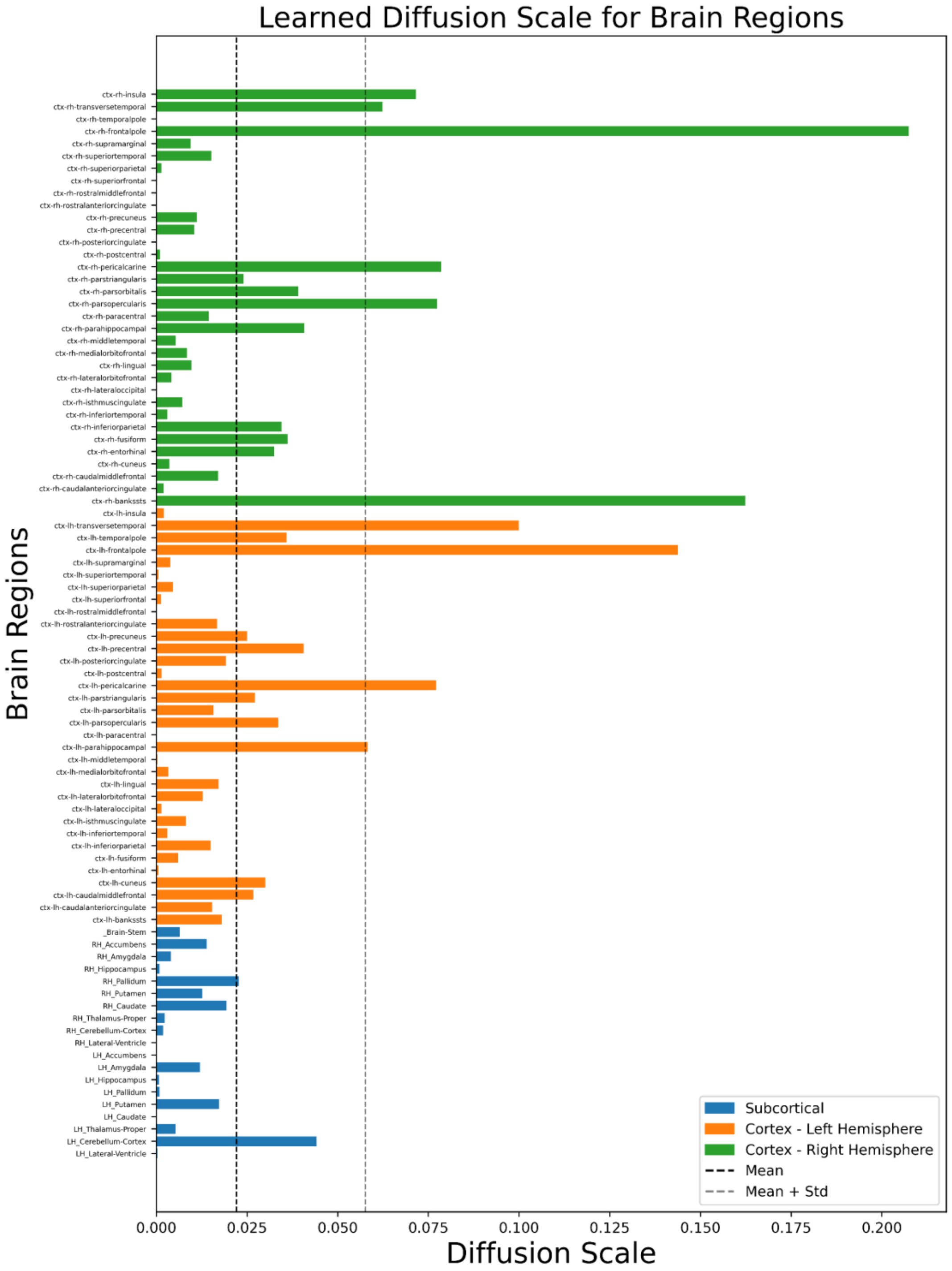
k (No. Eigenvectors)	MLP	Pearson's Correlation			MSE		
		Train Set	Validation Set	Test Set	Train Set	Validation Set	Test Set
87	Linear	0.8332 ± 0.0014	0.8318 ± 0.0059	0.8326 ± 0.0017	0.0220 ± 0.0004	0.0228 ± 0.0017	0.0223 ± 0.0004
	64	0.8314 ± 0.0008	0.8269 ± 0.0016	0.8283 ± 0.0004	0.0223 ± 0.0003	0.0236 ± 0.0006	0.0225 ± 0.0005
75	Linear	0.8292 ± 0.0010	0.8224 ± 0.0079	0.8267 ± 0.0013	0.0224 ± 0.0004	0.0241 ± 0.0016	0.0226 ± 0.0004
	64	0.8277 ± 0.0010	0.8237 ± 0.0039	0.8254 ± 0.0006	0.0224 ± 0.0003	0.0231 ± 0.0020	0.0228 ± 0.0003
64	Linear	0.8200 ± 0.0006	0.8133 ± 0.0048	0.8171 ± 0.0003	0.0230 ± 0.0006	0.0241 ± 0.0017	0.0233 ± 0.0005
	64	0.8237 ± 0.0019	0.8180 ± 0.0036	0.8206 ± 0.0012	0.0226 ± 0.0007	0.0237 ± 0.0016	0.0231 ± 0.0008

Jain, Chirag, Sravanthi Upadrasta Naga Sita, Avinash Sharma, and Bapi Raju Surampudi. "Diffusion wavelets on connectome: Localizing the sources of diffusion mediating structure-function mapping using graph diffusion wavelets." *Network Neuroscience* (2025): 1-21.

Results

- RoIs:
  - Frontal pole
  - Transverse-temporal
- Resting State Brain Networks
  - DMN





Chirag et al. *Network Neuroscience* (2025): 1-21.

Results

- Hub: Dense, long-distance connections to other regions
- Bilaterally Symmetric: Frontal and Temporal Poles

Table S1. Top 10 Brain Regions by Diffusion Scale (Sorted High to Low)

Brain Region	Diffusion Scale
ctx-rh-frontalpole	0.207406
ctx-rh-bankssts	0.162382
ctx-lh-frontalpole	0.143831
ctx-lh-transversetemporal	0.099931
ctx-rh-pericalcarine	0.078568
ctx-rh-parsopercularis	0.077401
ctx-lh-pericalcarine	0.077179
ctx-rh-insula	0.071619
ctx-rh-transversetemporal	0.062333
ctx-lh-parahippocampal	0.058326

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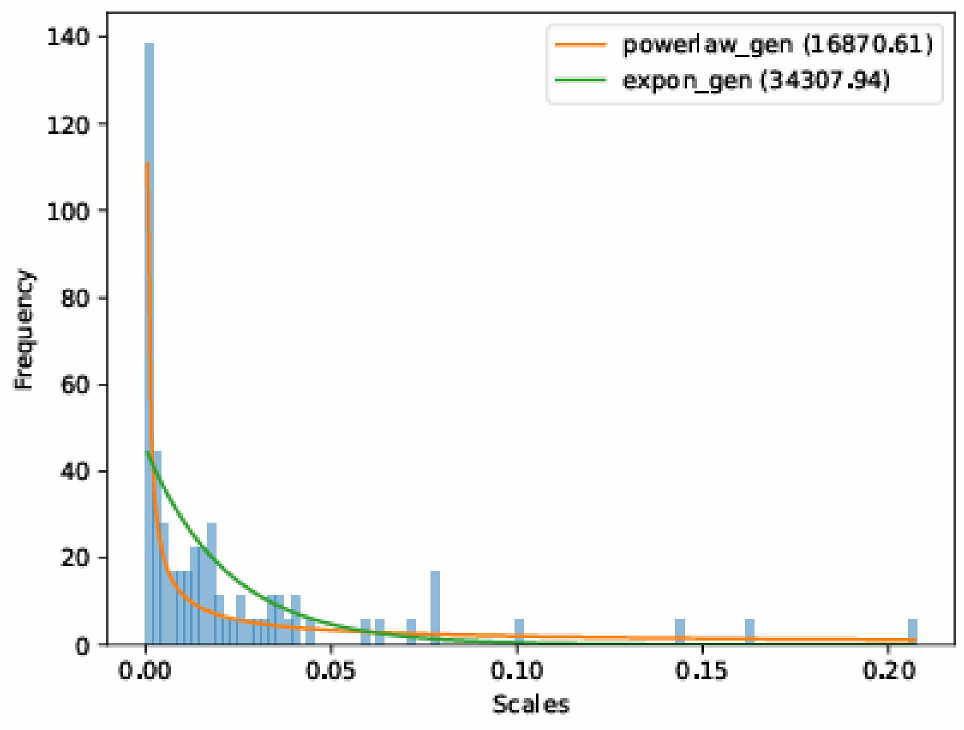
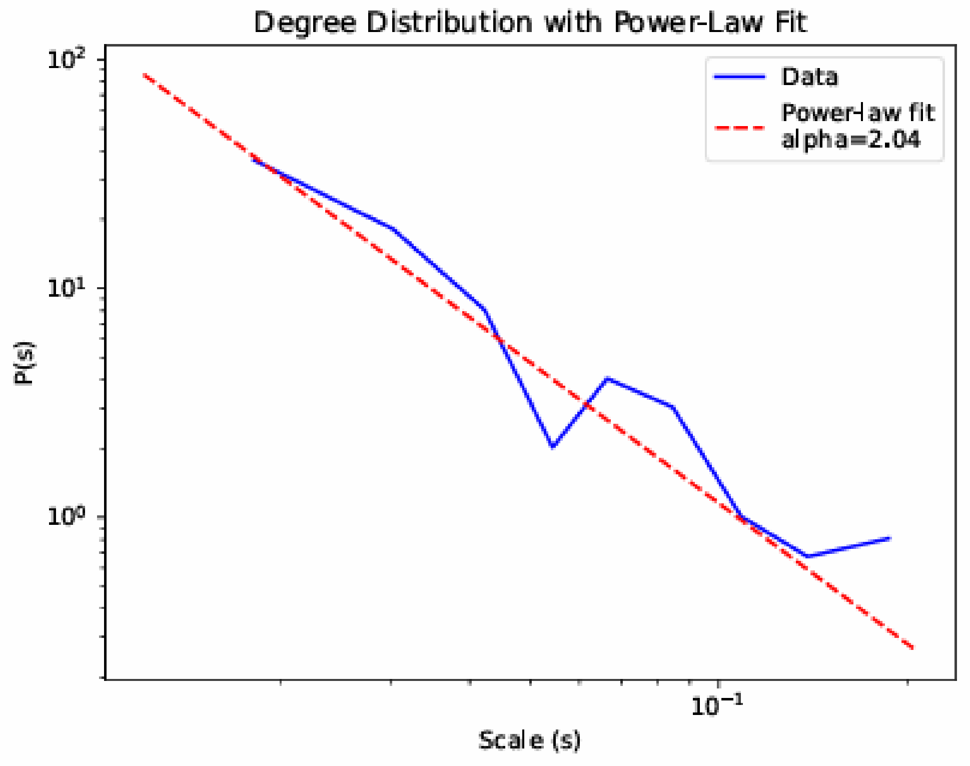
Achard, Sophie, et al. "A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs." *Journal of Neuroscience* 26.1 (2006): 63-72.

Results: Power Law & Criticality





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Summary and Future Directions

- Spectral Graph Theory is an important tool in Network Neuroscience
  - Enables capturing higher-order interactions
  - Resolving the discordance between SC and FC
- Graph Algorithms are instrumental in analysis of brain networks.
- Future Directions:
  - Healthy Aging & Disease characterization
  - Task-fMRI data analysis
  - Temporal Dynamics using Diffusion Model [Surampudi et al., tMKL. *Neuroimage*, 2019]
  - The power of learning can be utilized with Graph Neural Networks (GNNs) [Oota et al., AGHN. *Scientific Reports* 2024]

Acknowledgements

Joyneel Misra, BTech (Hons.)
Subba Reddy Oota, MTech

Shruti Naik, MS
Govinda Surampudi, MS
Archi Yadav, MS
Arpita Dash, MS Dual
Chirag Jain, MS Dual

Dipanjan Roy, IIT-J
Avinash Sharma, IIT-J