Feb. 19. 2025

Charting Multi-Scale Brain Phenotypes Using

Spectral Normative Models

Presentation slides for the ISMRM Workshop on 40 Years of Diffusion

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National University of Singapore & The University of Melbourne

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Declaration of Financial Interests or Relationships

Speaker Name: Sina Mansour L.

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Overview

→ Big data in brain imaging, and the importance of dimensionality reduction

A primer on Graph Signal Processing (GSP)

Diffusion MRI and brain connectivity eigenmodes

Leveraging eigenmodes for Spectral Normative Modeling (SNM)

Empirical application: personalized brain charting of Alzheimer's Disease

Concluding remarks and future directions

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→ Brain scans are inherently large files

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→ Sample sizes are limited relative to exemplary AI models

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Example	
Total data	
Tokens (sample size)	
Single token size	

Big data in brain imaging

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Example	deepseek
Total data	45 terabytes
Tokens (sample size)	~15 trillion
Single token size	~3 bytes

Big data in brain imaging

Brain scans are inherently large files

Sample sizes are limited relative to exemplary AI models

Example	deepseek	Stable Diffusion
Total data	45 terabytes	400 terabytes
Tokens (sample size)	~15 trillion	~2 billion
Single token size	~3 bytes	~200 kilobytes

Big data in brain imaging

Brain scans are inherently large files

Sample sizes are limited relative to exemplary AI models

Example	deepseek	Stable Diffusion	biobank uk
Total data	45 terabytes	400 terabytes	90 terabytes
Tokens (sample size)	~15 trillion	~2 billion	~45 thousand
Single token size	~3 bytes	~200 kilobytes	~2 gigabytes

Big data in brain imaging

Brain scans are inherently large files

Sample sizes are limited relative to exemplary AI models

→ Importance of dimensionality reduction for AI in neuroimaging

Graph Signal Processing (GSP)

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→ A field of signal processing dedicated to analyzing signals on graphs

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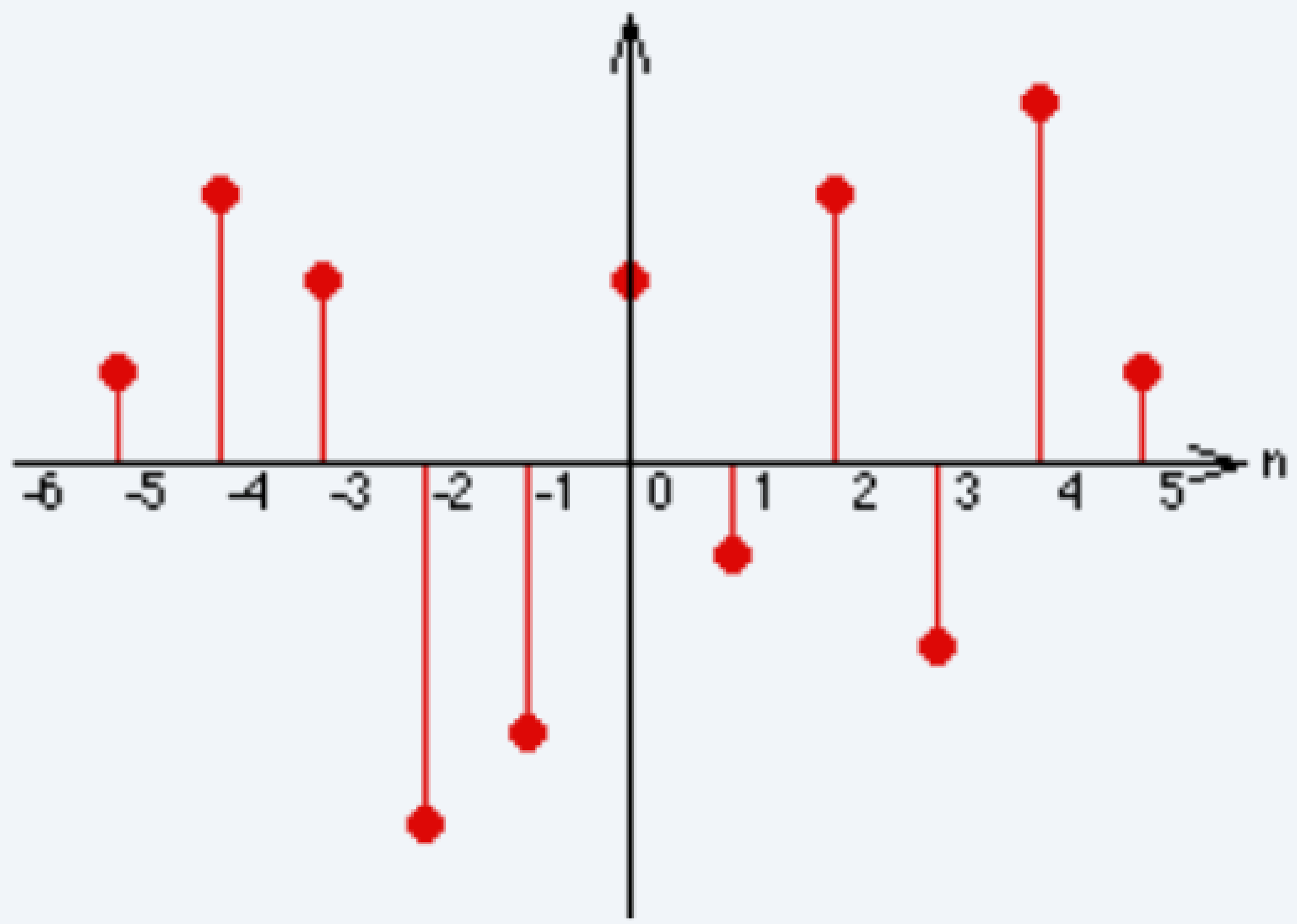
A field of signal processing dedicated to analyzing signals on graphs

Discrete-time signal



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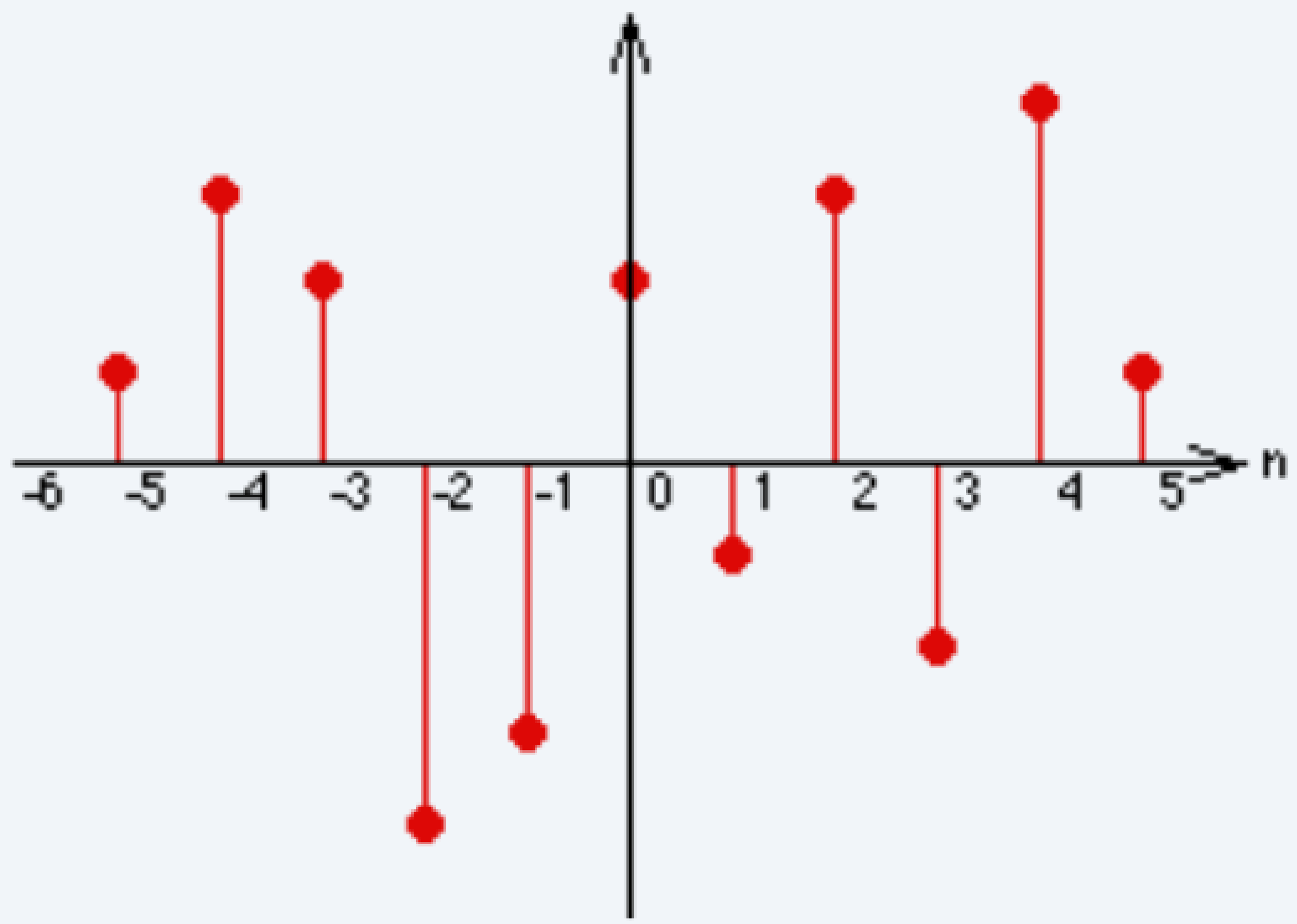
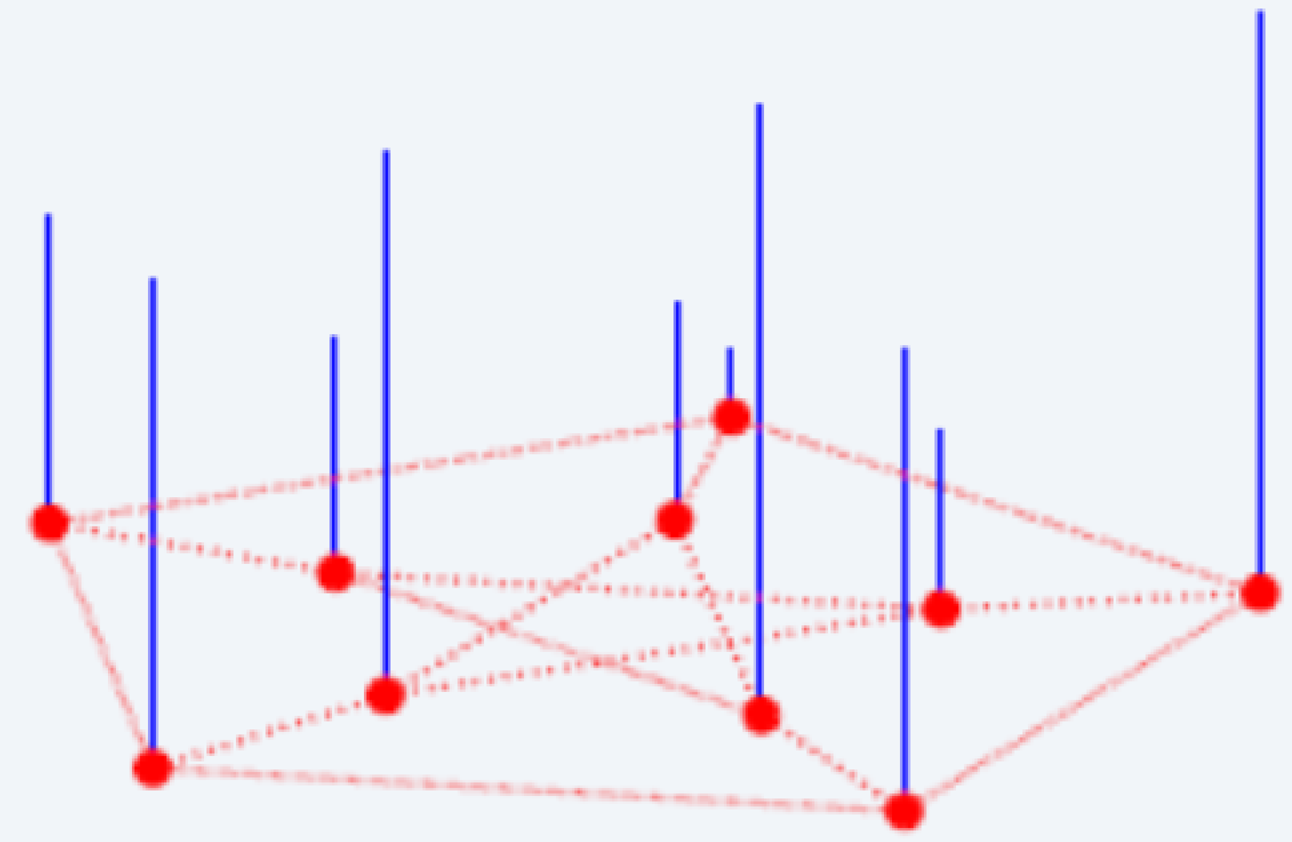


Graph Signal: Vector of values over the nodes



Shuman et al. (2013)

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→ Generalization of discrete signal processing ideas to the realm of networks

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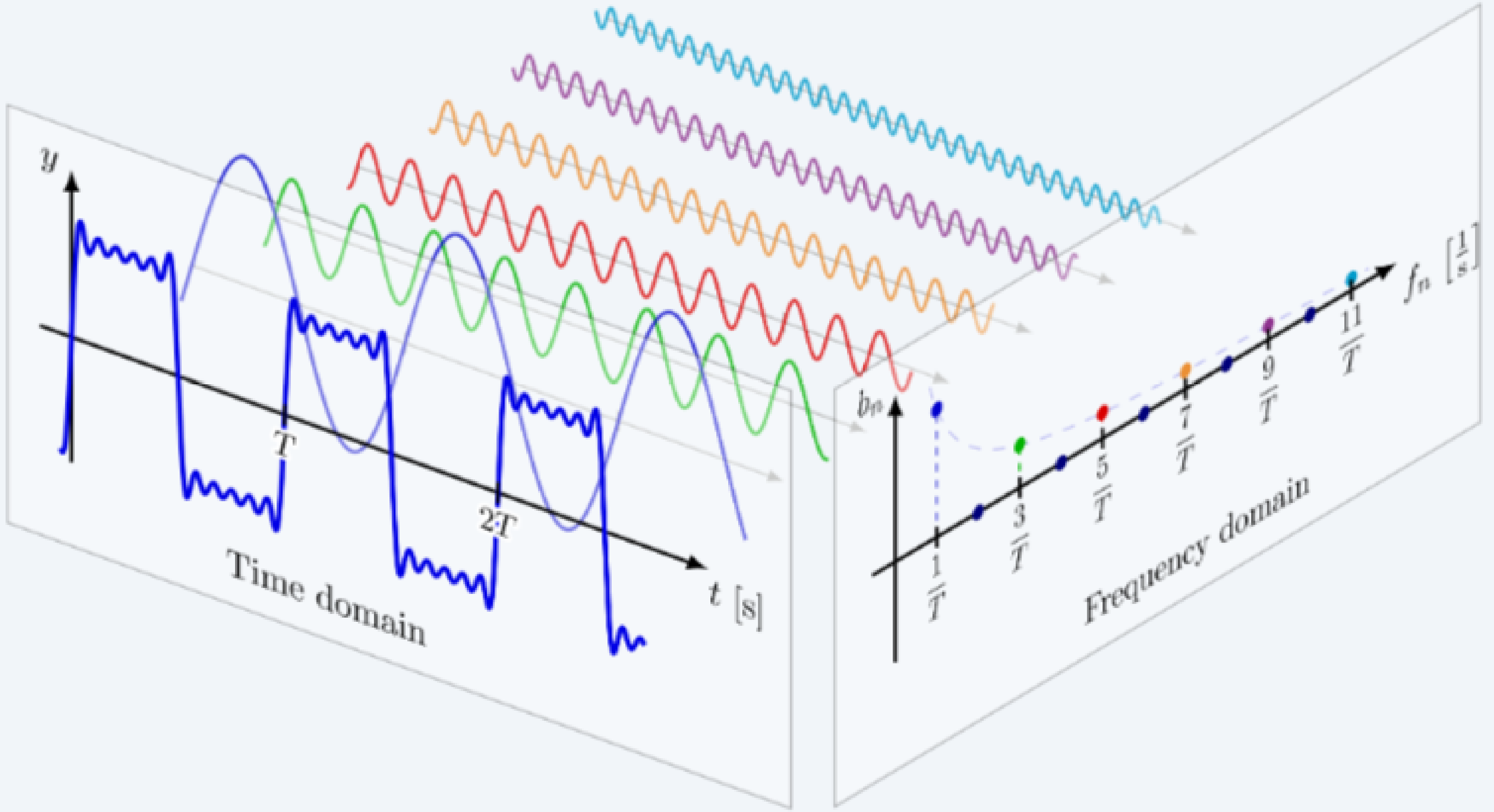
Discrete Fourier Transform

$$X_k = \sum_{n=0}^{N-1} x_n \cdot e^{-\frac{i2\pi}{N}kn}$$



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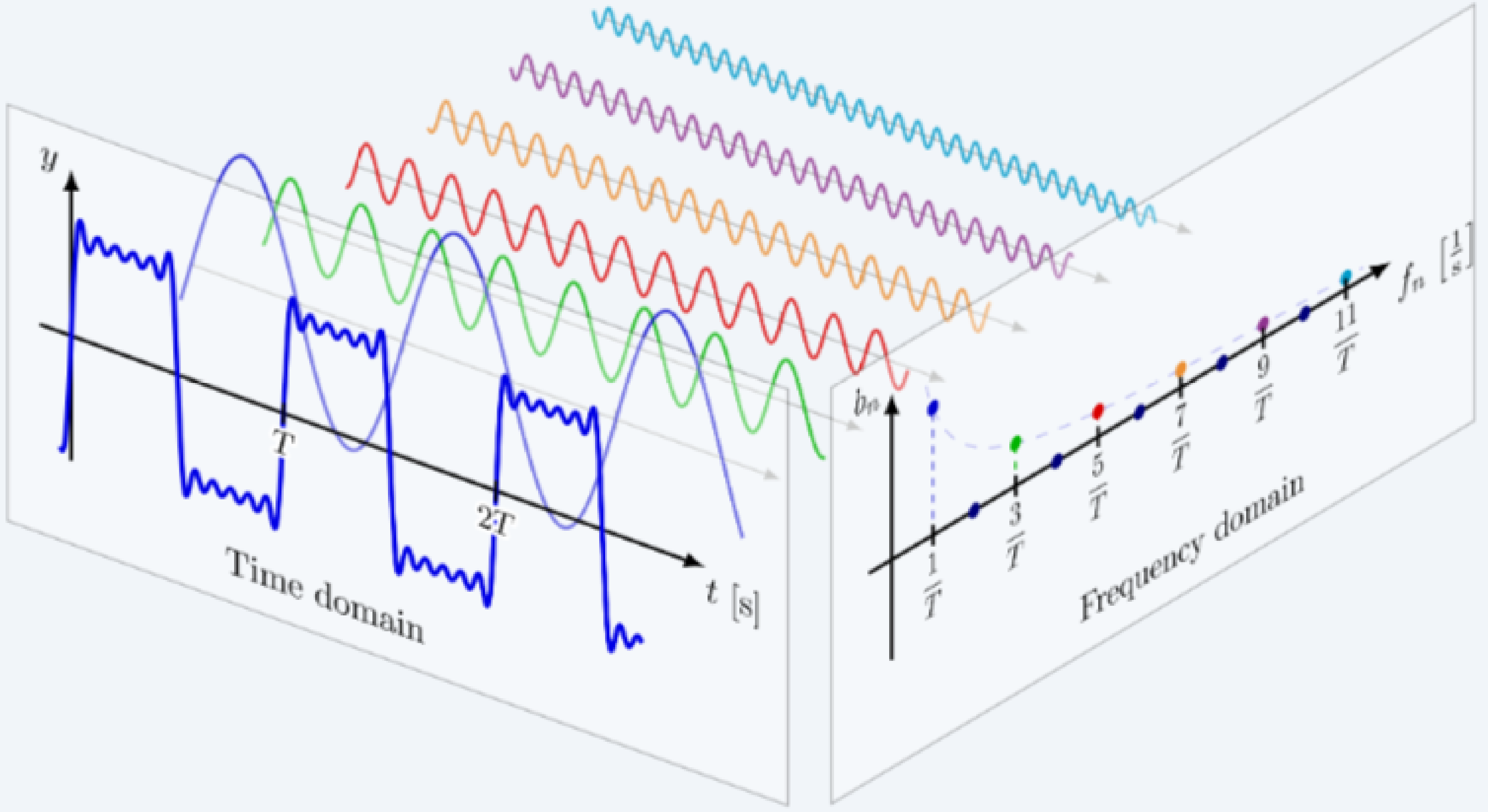
Time domain



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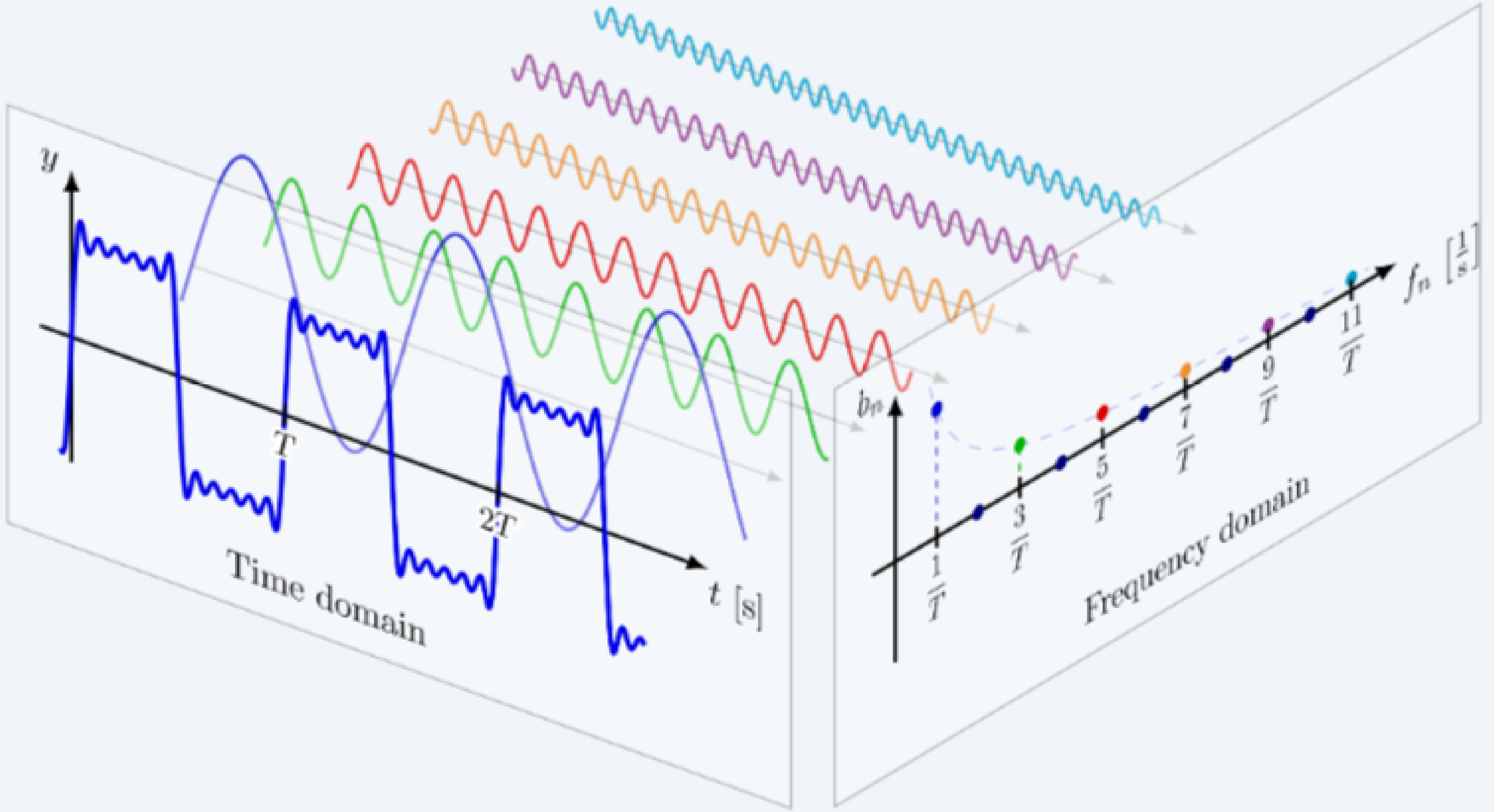
Frequency domain

Time domain



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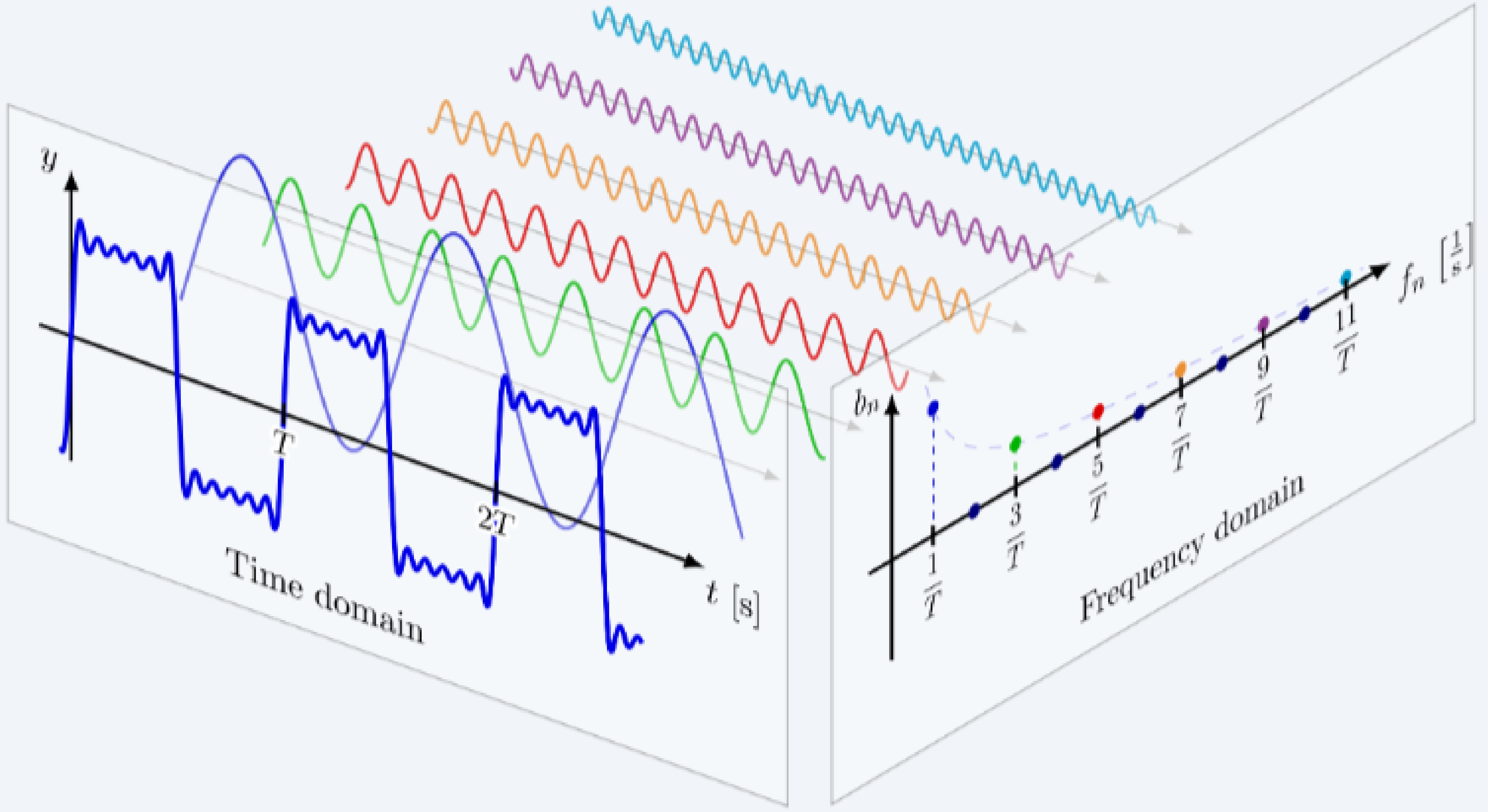
Inverse Discrete Fourier Transform

$$x_n = \frac{1}{N} \sum_{k=0}^{N-1} X_k \cdot e^{i2\pi kn/N}$$



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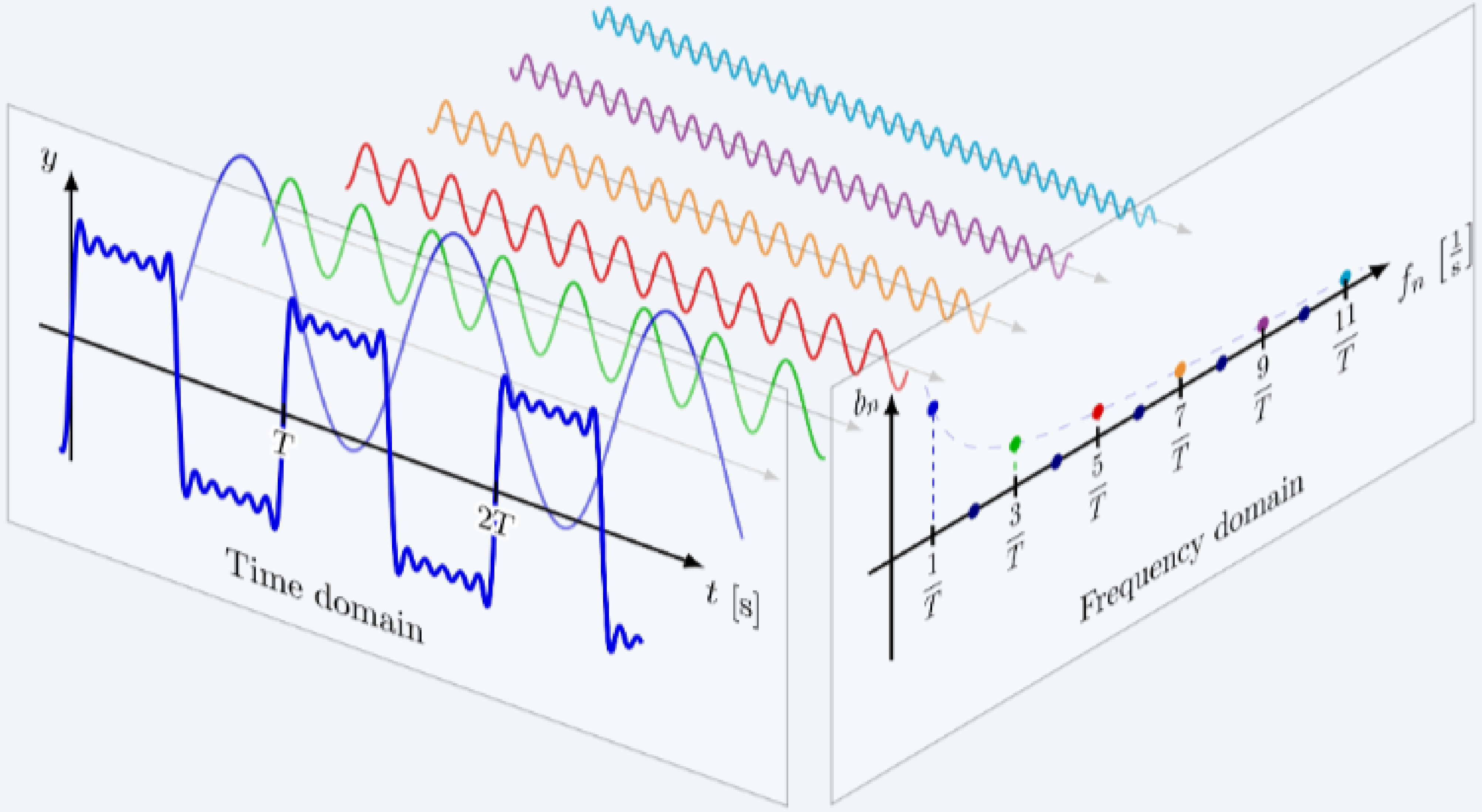

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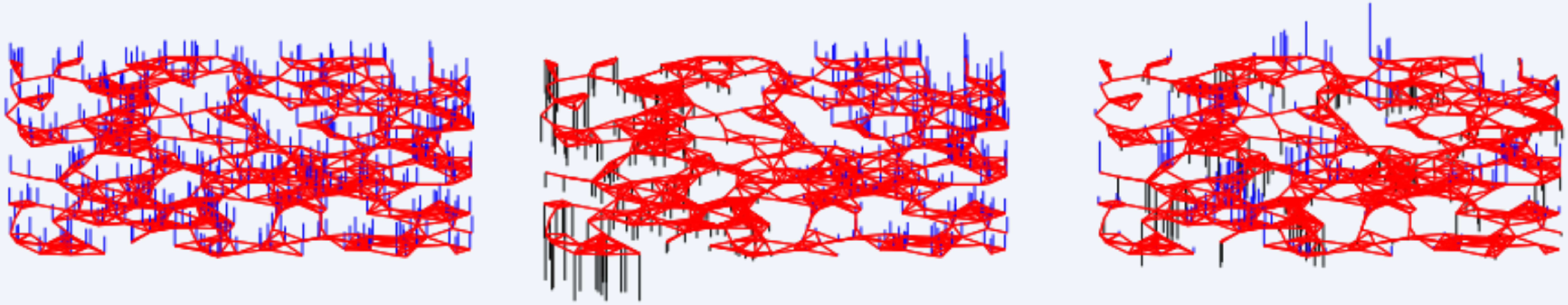
→ Analogous to DFT, but for graphs



Lower graph frequency

Higher graph frequency

Graph Fourier Transform (GFT)

Analogous to DFT, but for graphs

→ GFT is defined using a graph shift operator

Shift Operator: symmetric normalized Laplacian

$$L^{\mathrm{sym}} := D^{-\frac{1}{2}} L D^{-\frac{1}{2}} = I - D^{-\frac{1}{2}} A D^{-\frac{1}{2}}$$

Graph Fourier Transform (GFT)

Analogous to DFT, but for graphs

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→ Graph Fourier basis via singular value decomposition of shift operator

$$\mathbf{S} = \mathbf{V}\boldsymbol{\Lambda}\mathbf{V}^{-1}$$

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Graph Fourier Transform

$$\tilde{\mathbf{x}} = \mathbf{V}^\top \mathbf{x}$$

Huang et al. (2018)

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Graph Filters

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→ Idea: Reconstruct particular frequency bands of the signal

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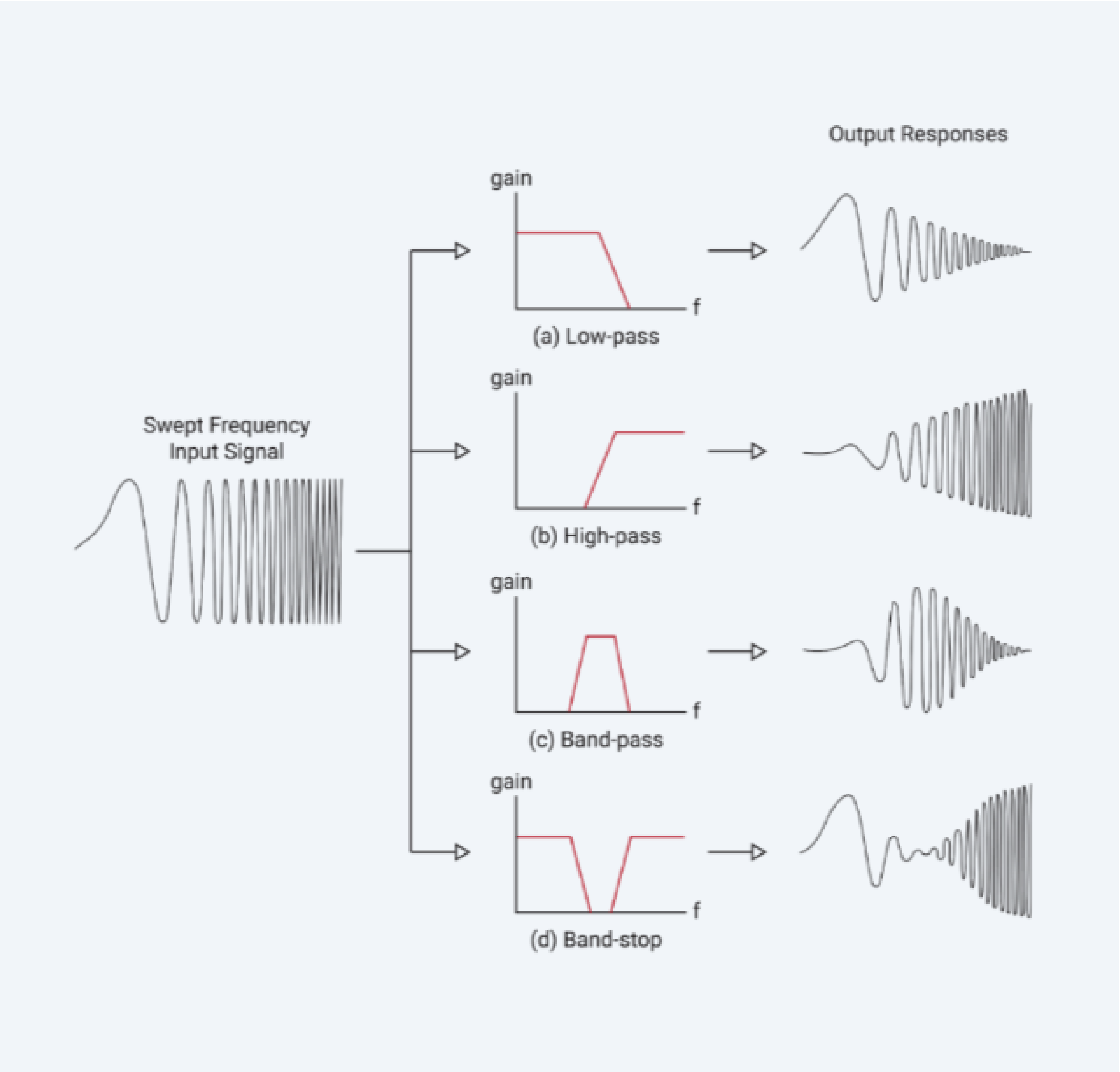
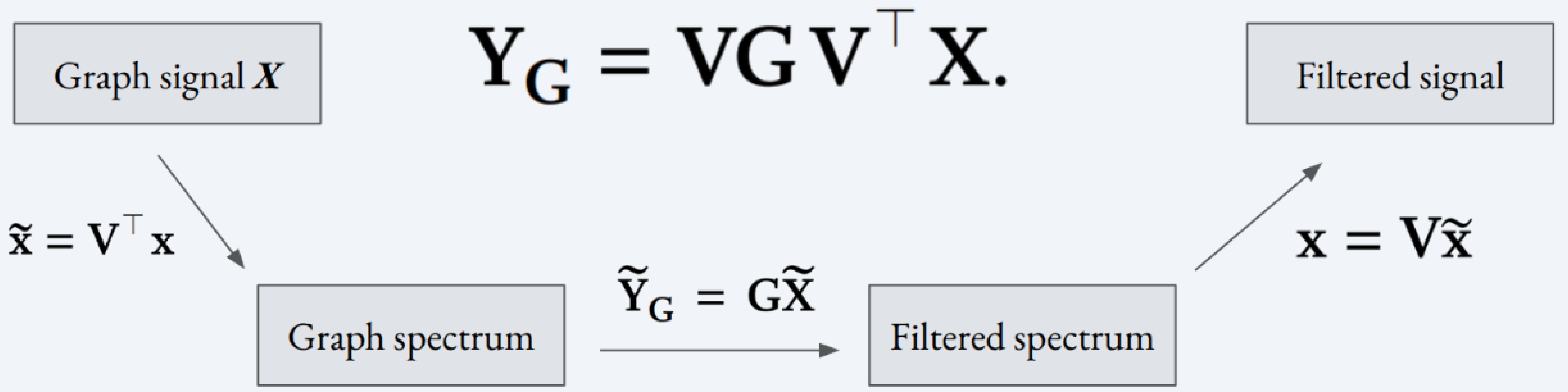


Graph Filters

Idea: Reconstruct particular frequency bands of the signal

Graph Filter G



Huang et al. (2018)

Graph Filters

Idea: Reconstruct particular frequency bands of the signal

Graph Filter G

$$\mathbf{Y_G} = \mathbf{V G V^\top X}.$$

Graph signal X

Filtered signal

$\tilde{\mathbf{x}} = \mathbf{V}^\top \mathbf{x}$

GFT

Graph spectrum

$\tilde{\mathbf{Y}}_\mathbf{G} = \mathbf{G}\tilde{\mathbf{X}}$

Filtering

Filtered spectrum

$\mathbf{x} = \mathbf{V}\tilde{\mathbf{x}}$

iGFT

Huang et al. (2018)

Network Neuroscience and GSP on brain graphs

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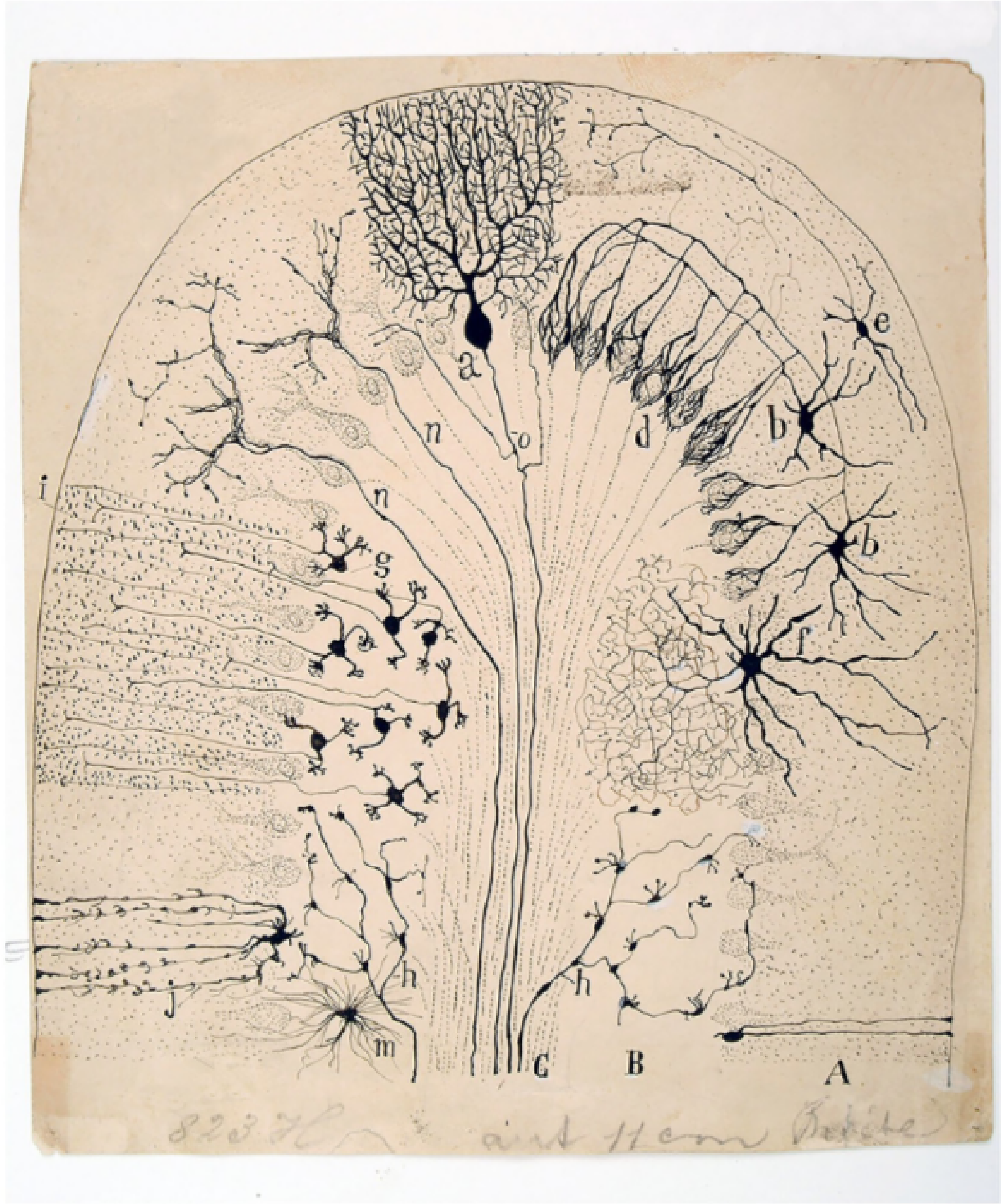
→ Modeling anatomical brain networks



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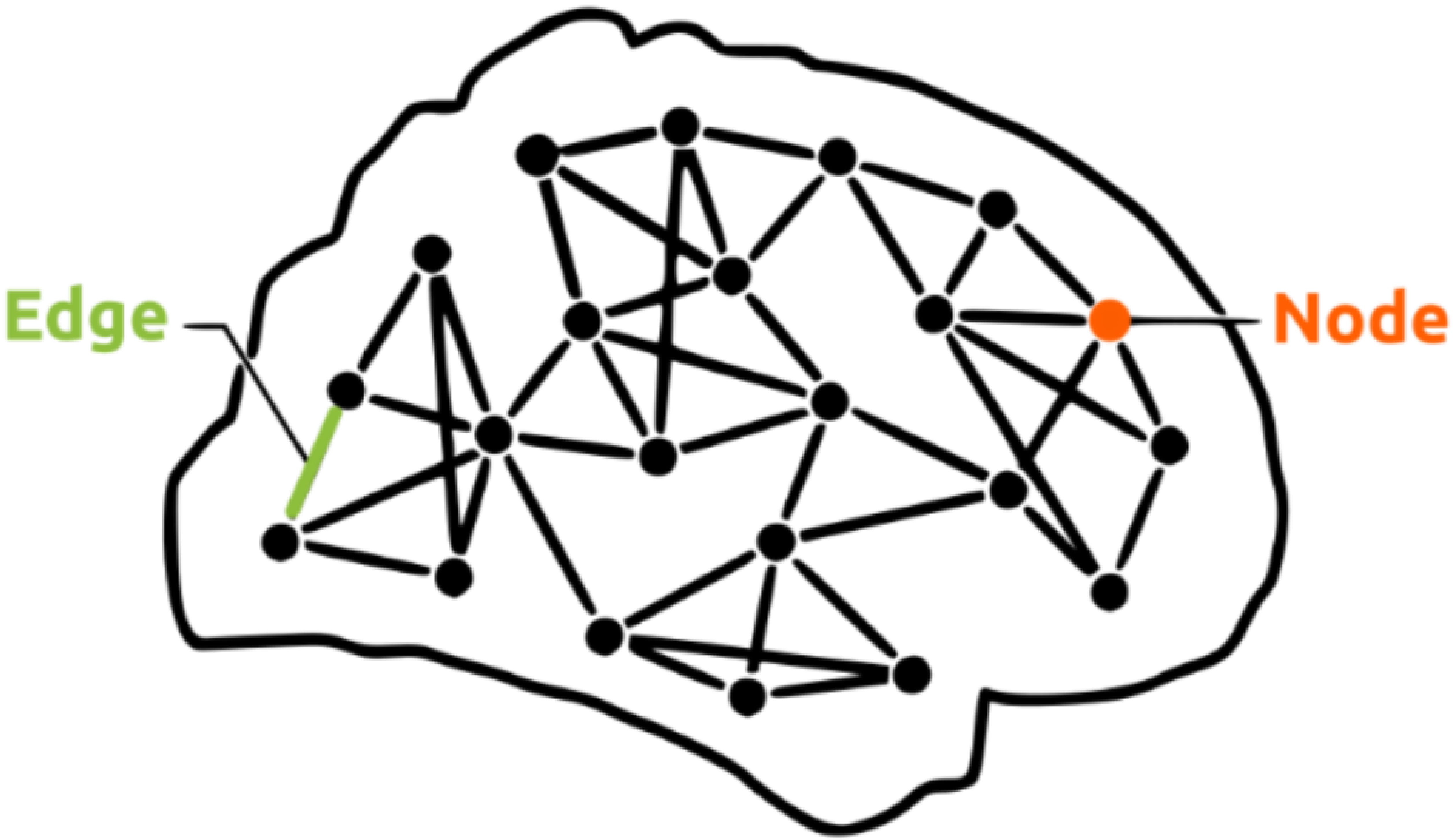
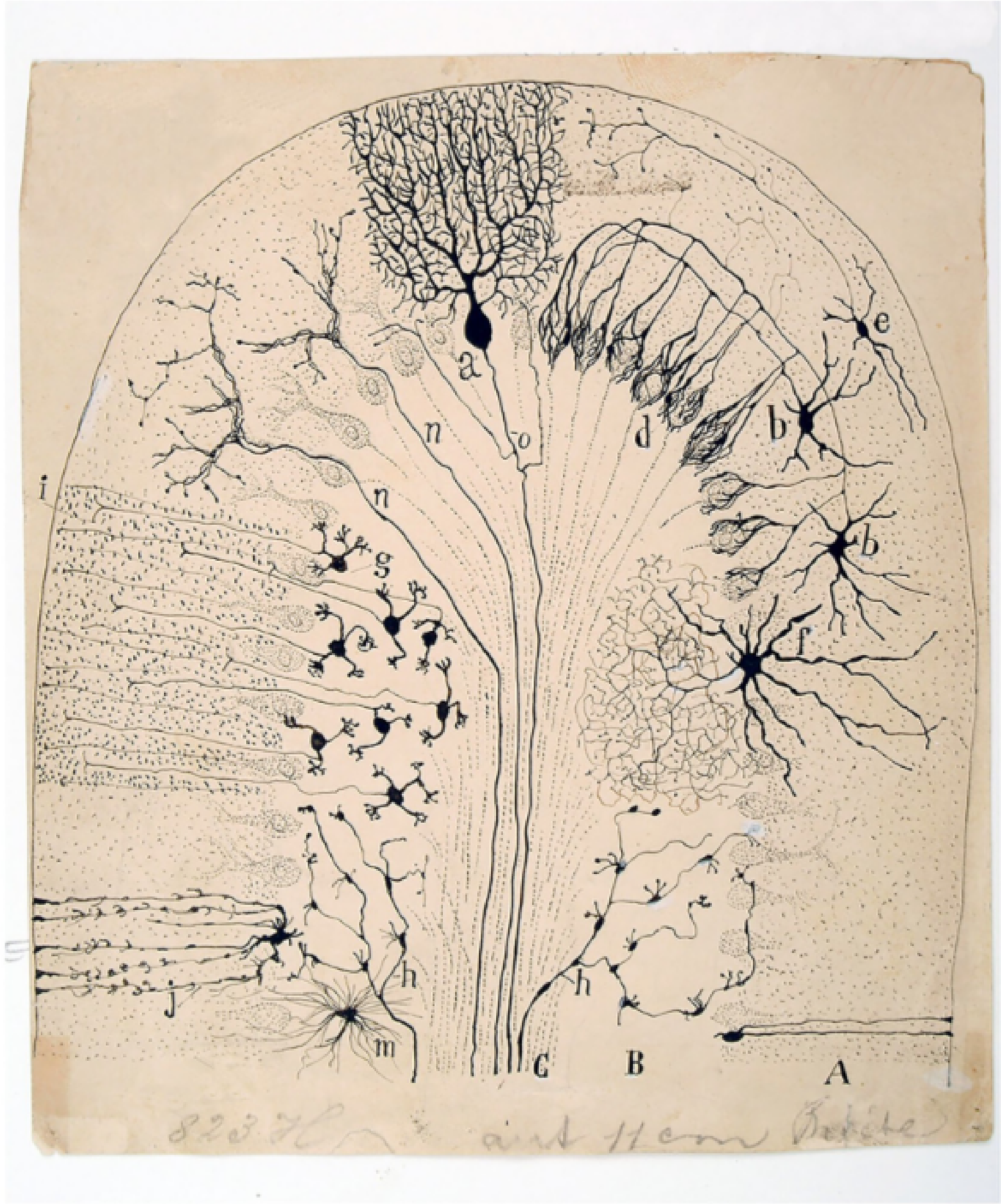
Modeling anatomical brain networks





Diffusion MRI data

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→ Enables mapping in-vivo anatomical wiring networks

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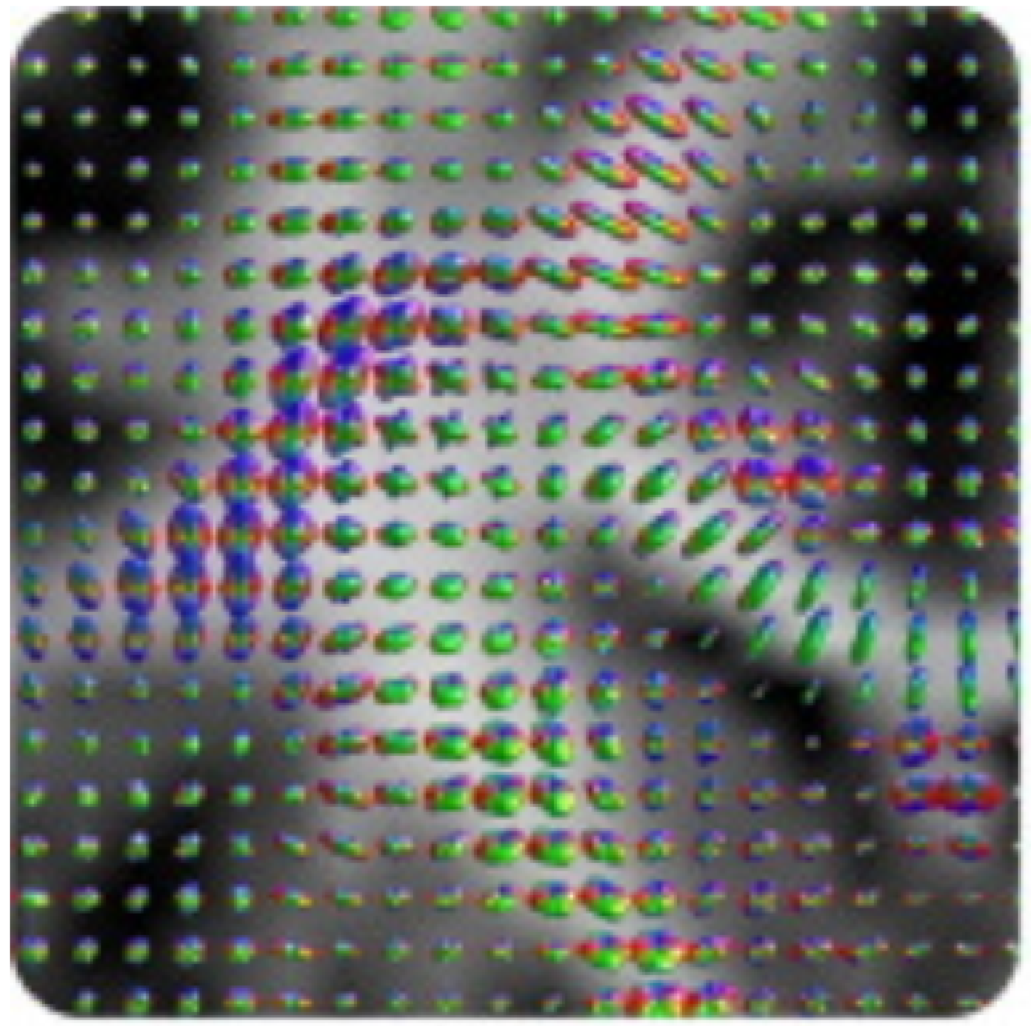
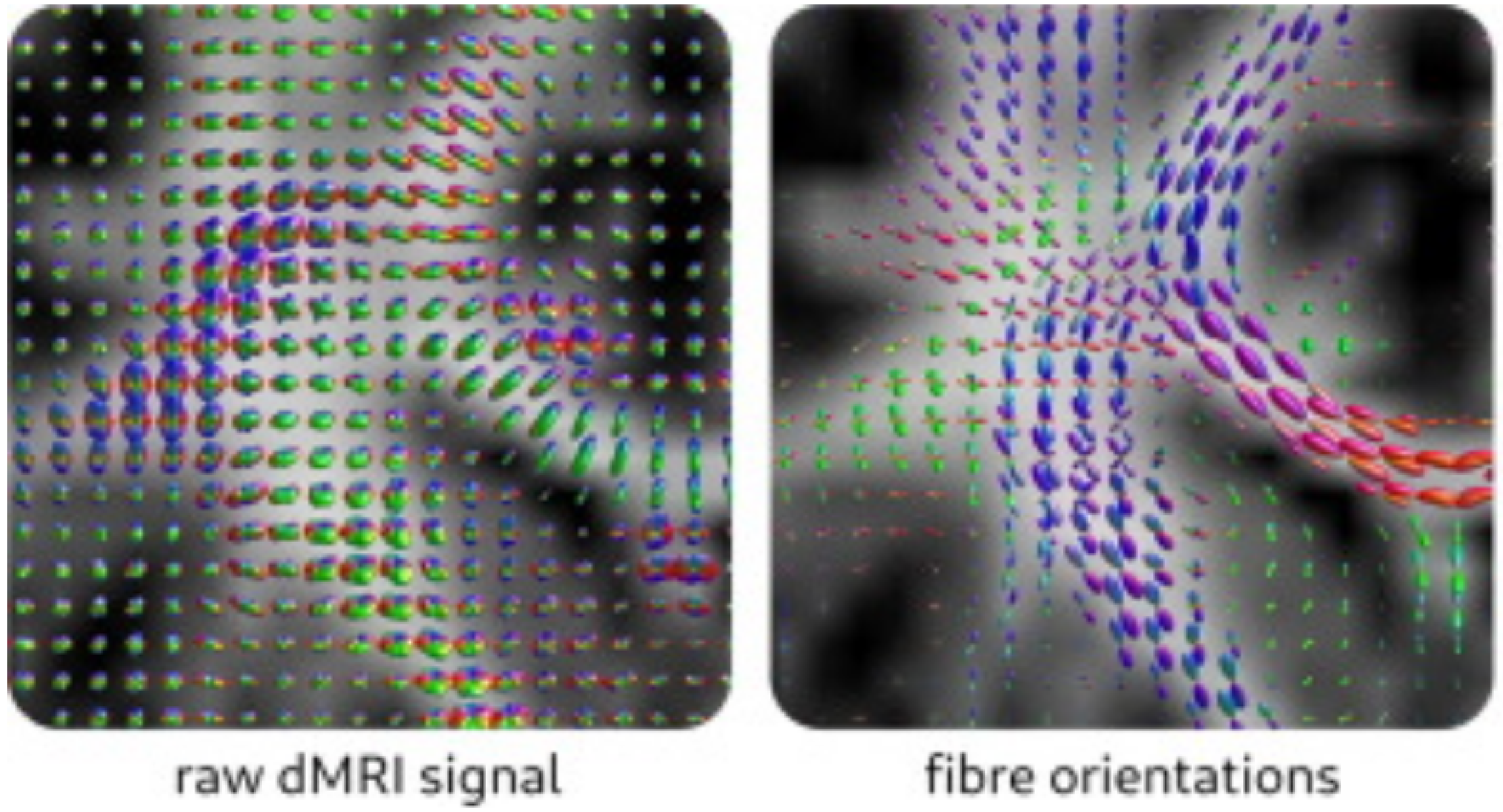


raw dMRI signal

Tournier 2019

Diffusion MRI data

Enables mapping in-vivo anatomical wiring networks



Tournier 2019

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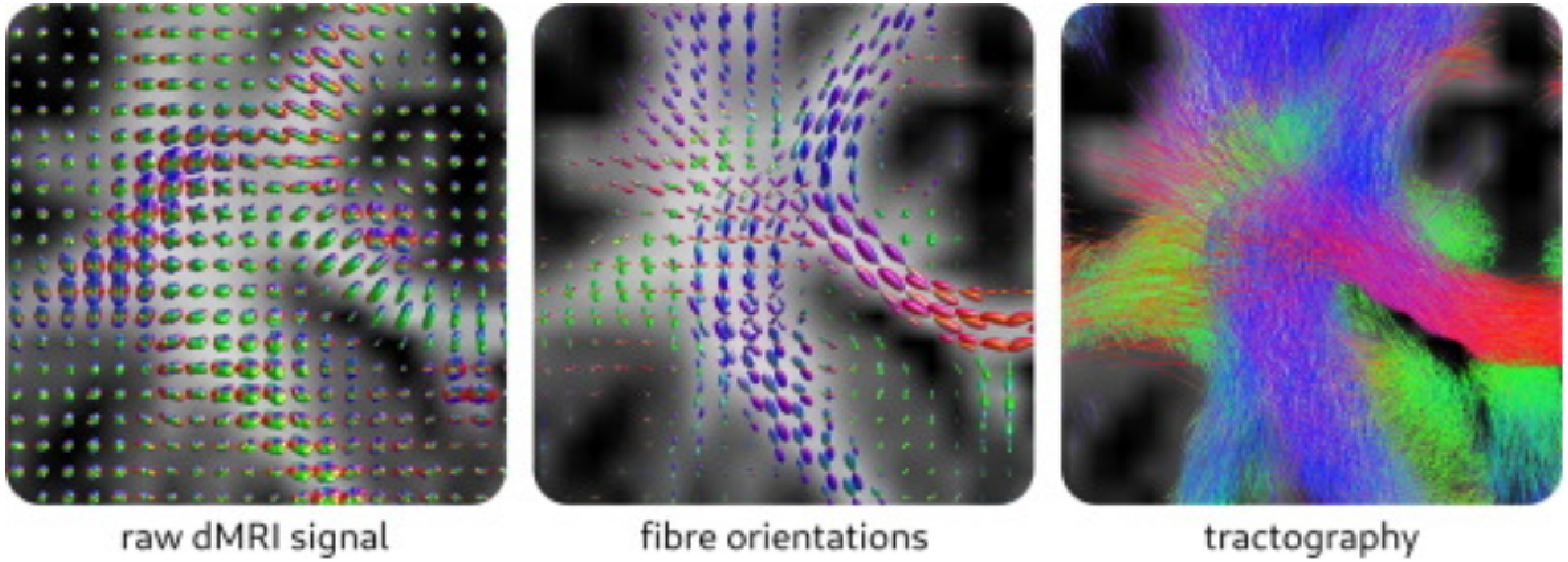

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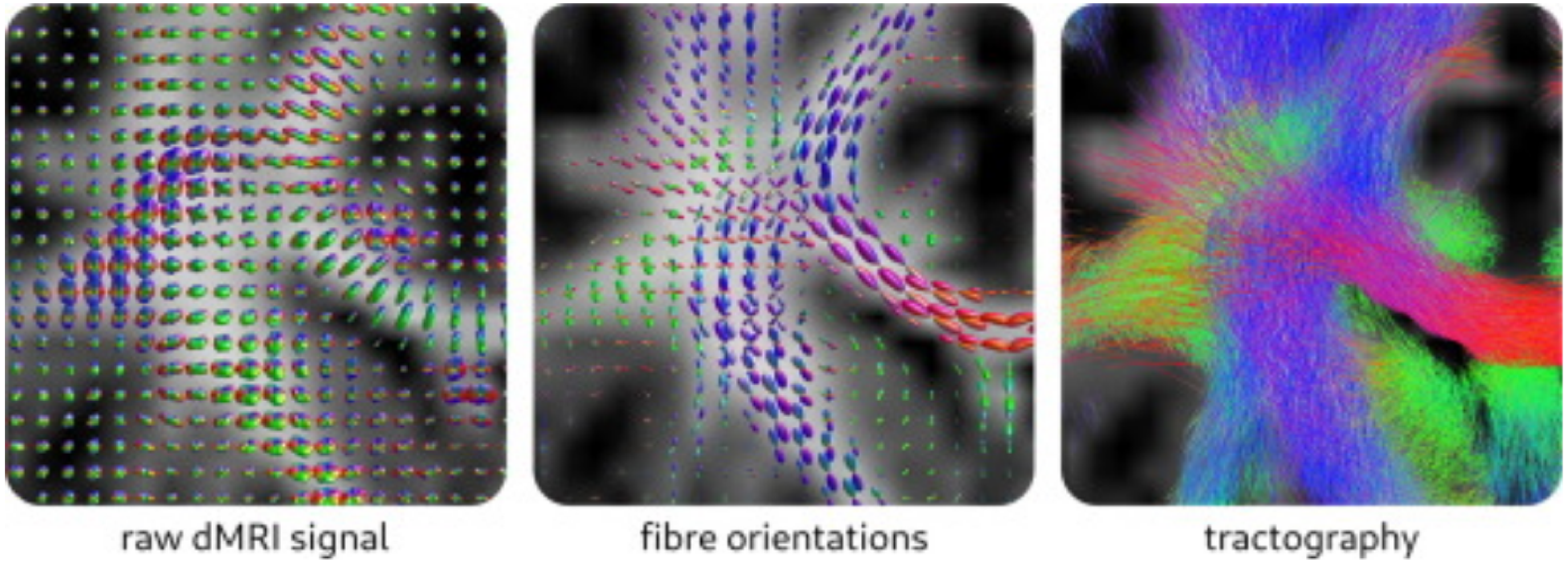

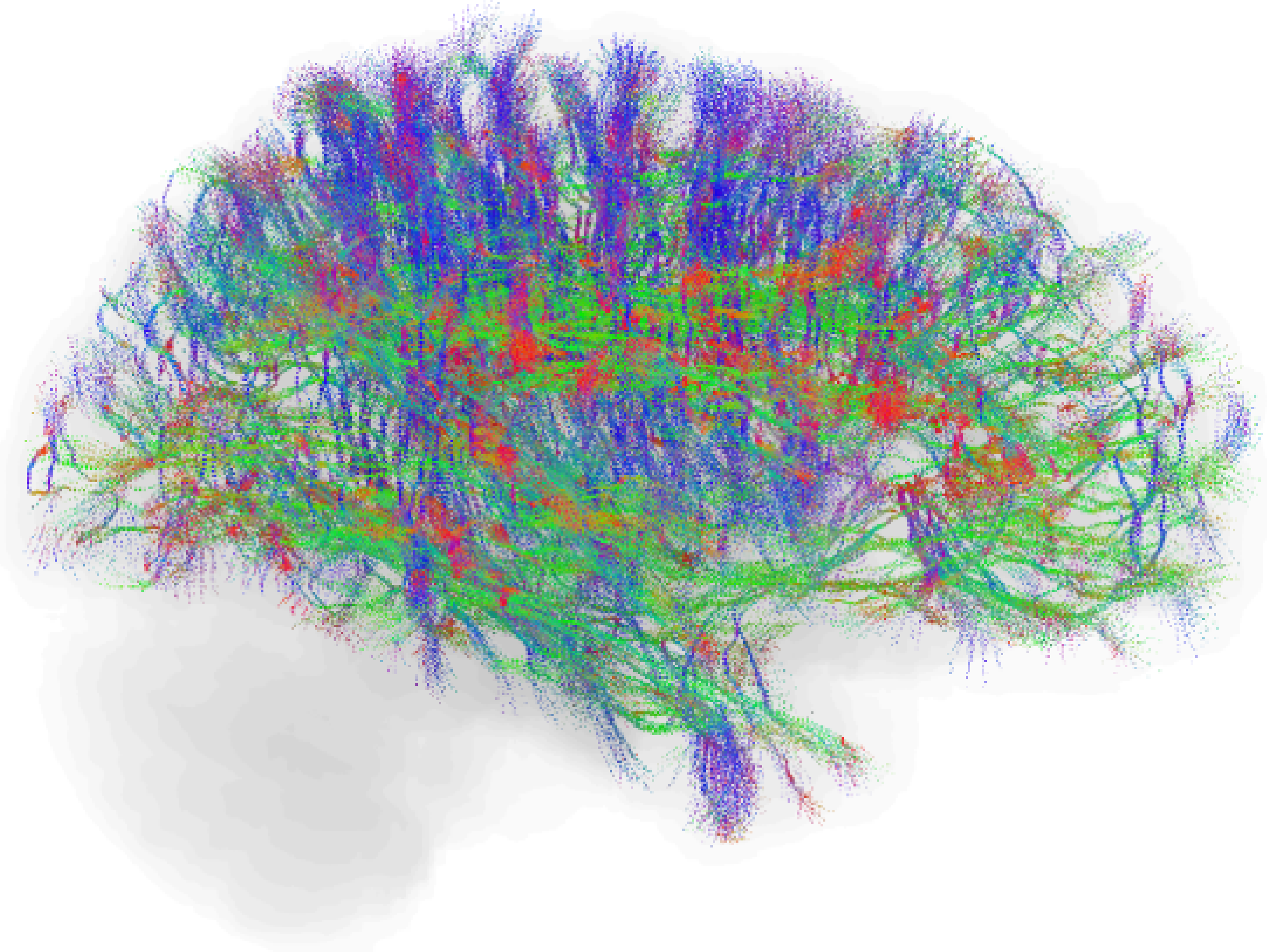

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GSP in brain imaging

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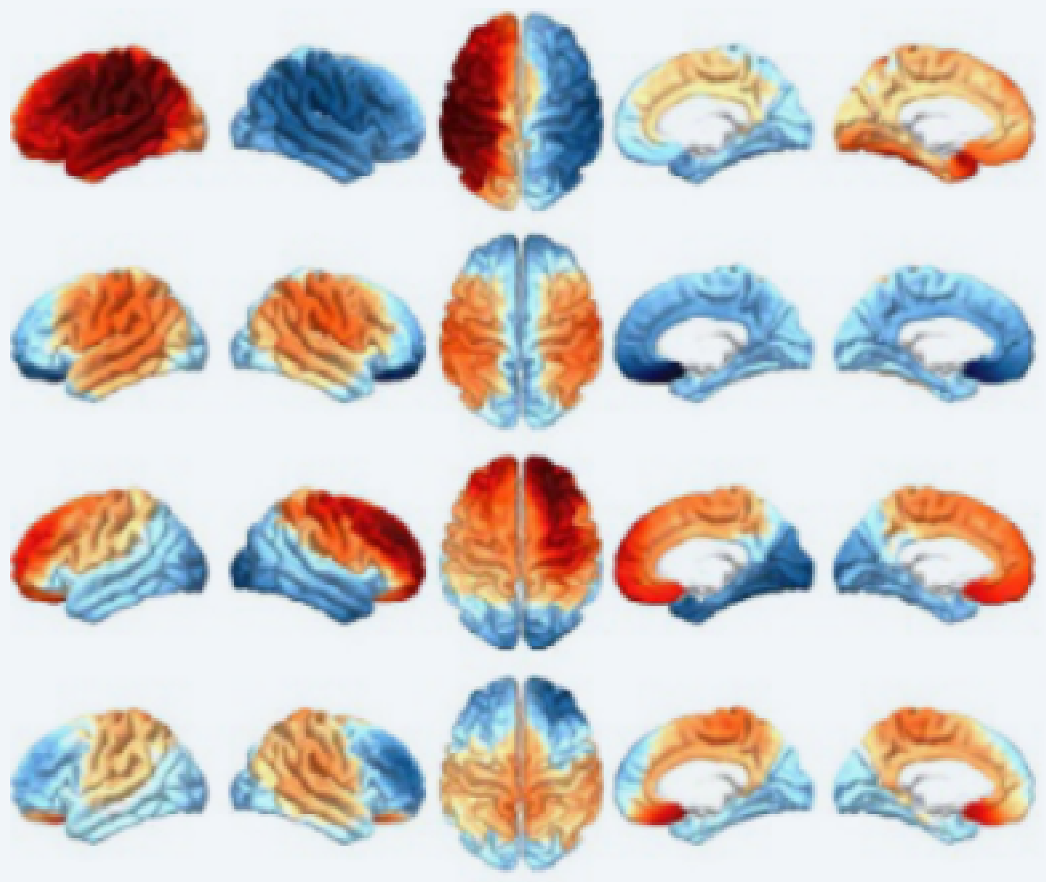
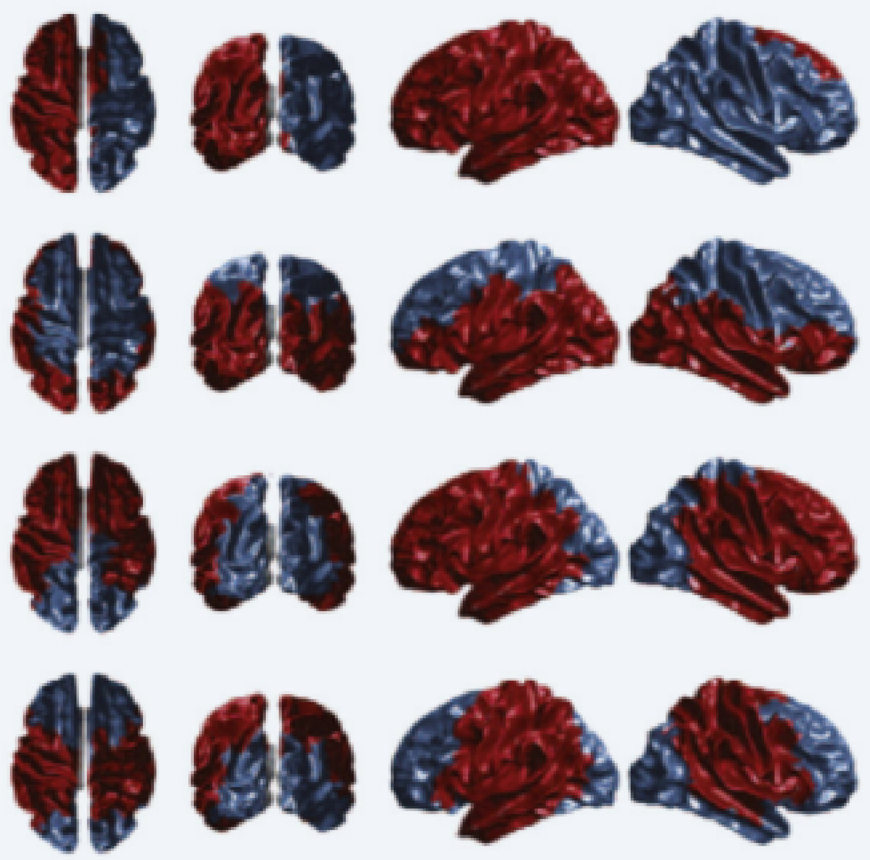
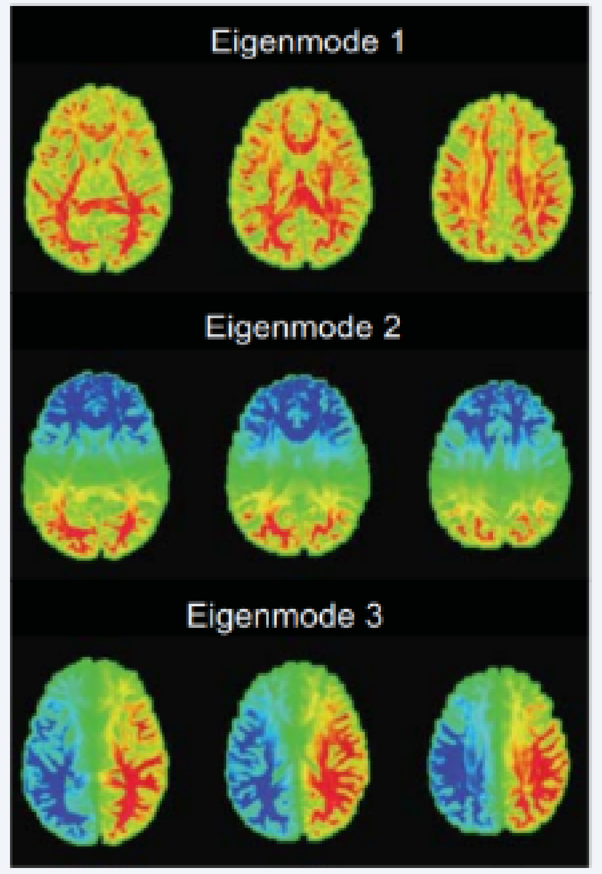
→ GSP methods have been used to study brain signals in the past decade



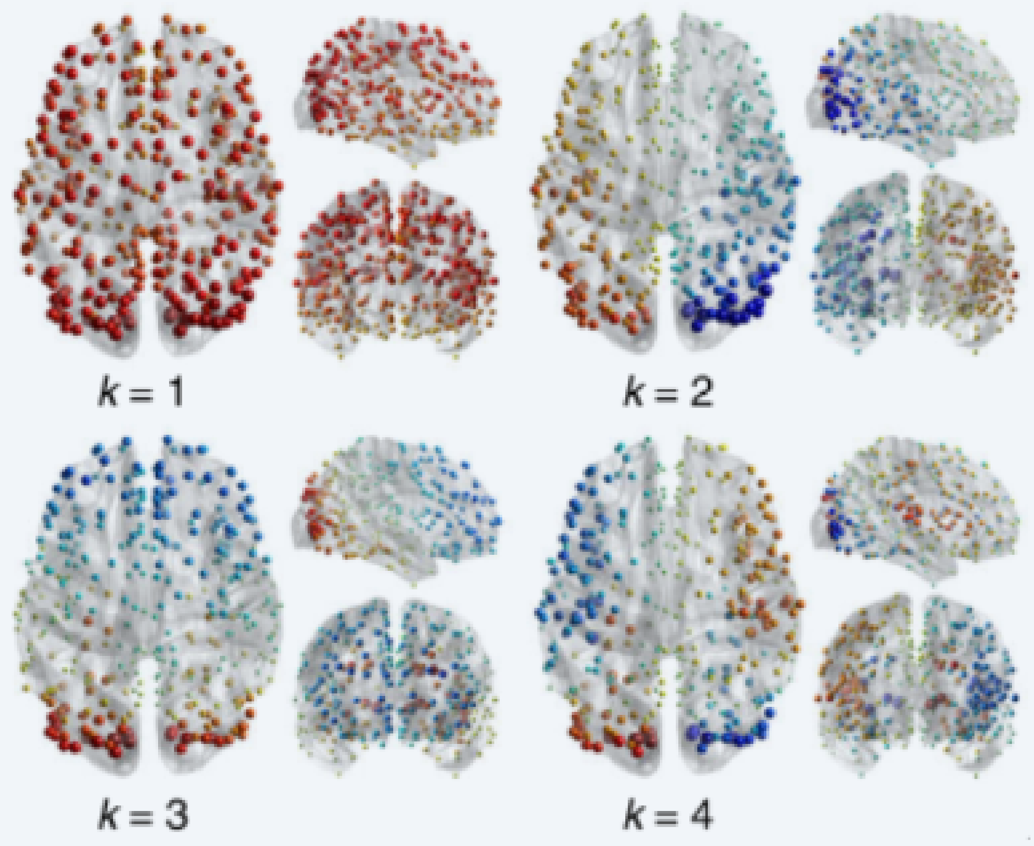
Atasoy et al. (2016)



Robinson et al. (2016)



Tarun et al. (2019)

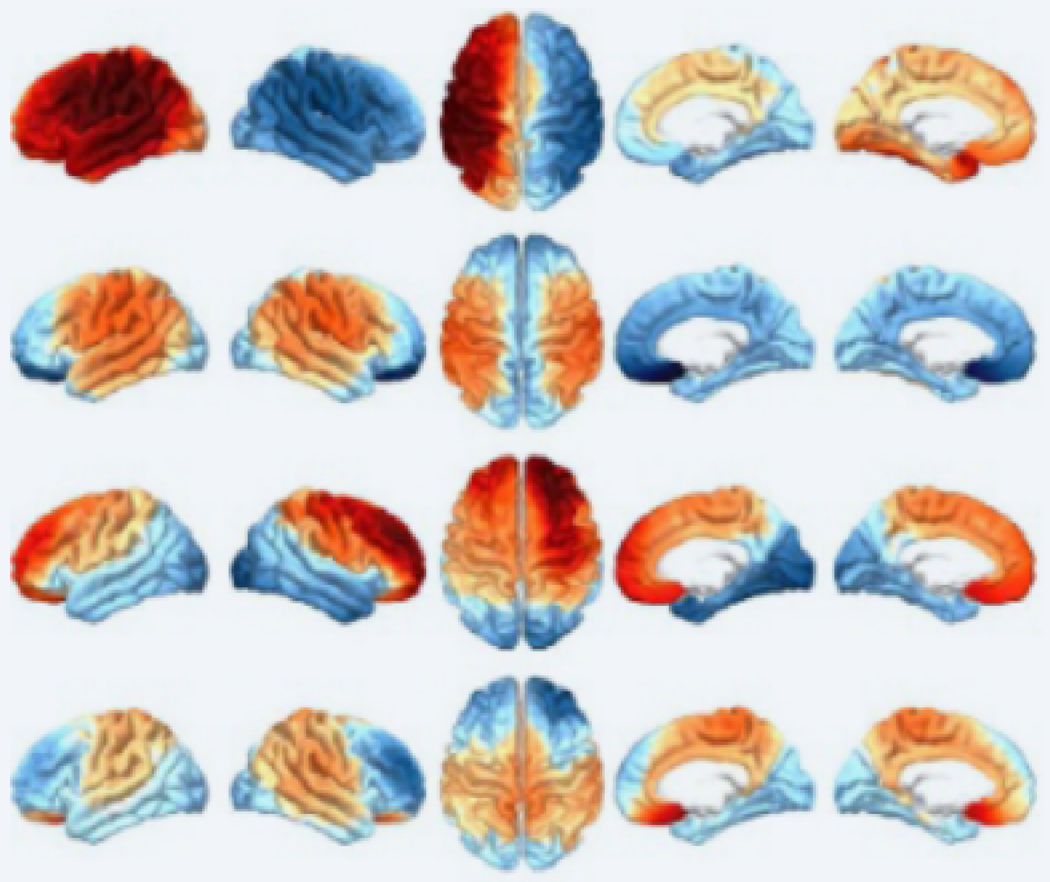


Preti et al. (2019)

GSP in brain imaging

GSP methods have been used to study brain signals in the past decade

→ Different terminologies: harmonics, eigenmodes, gradients, …



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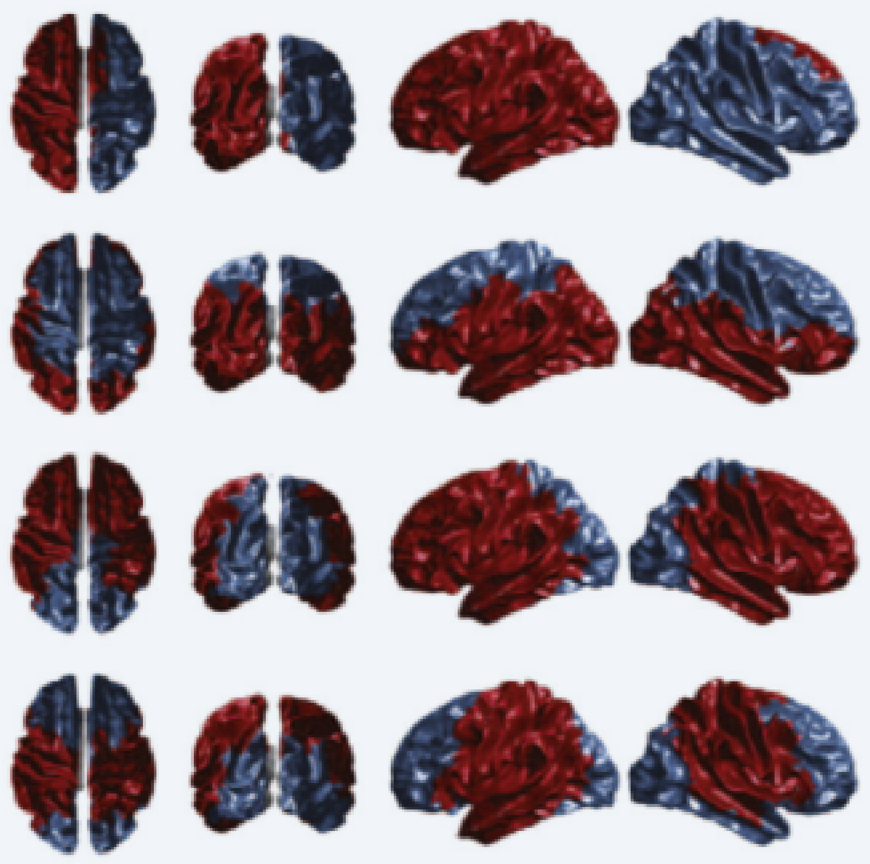

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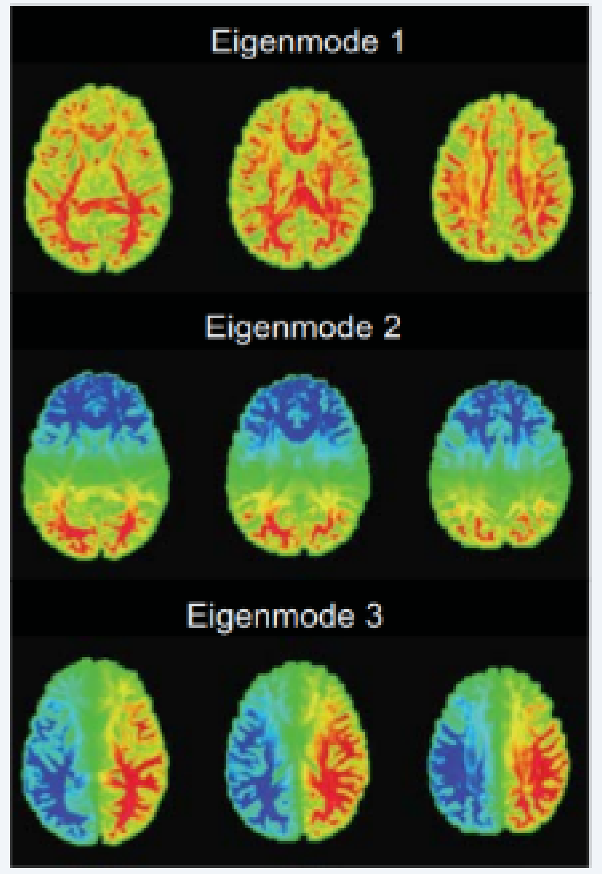

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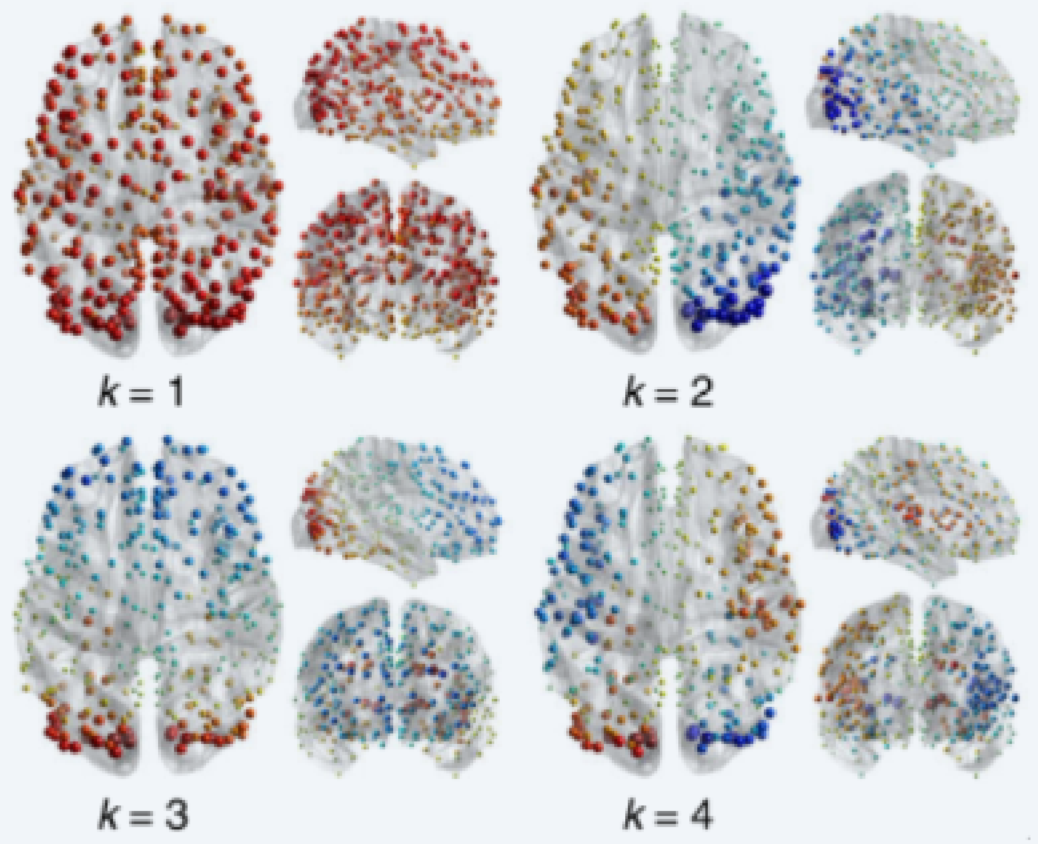

Preti et al. (2019)

High-resolution connectome eigenmodes

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→ Perform tractography over a large sample (e.g. HCP YA)

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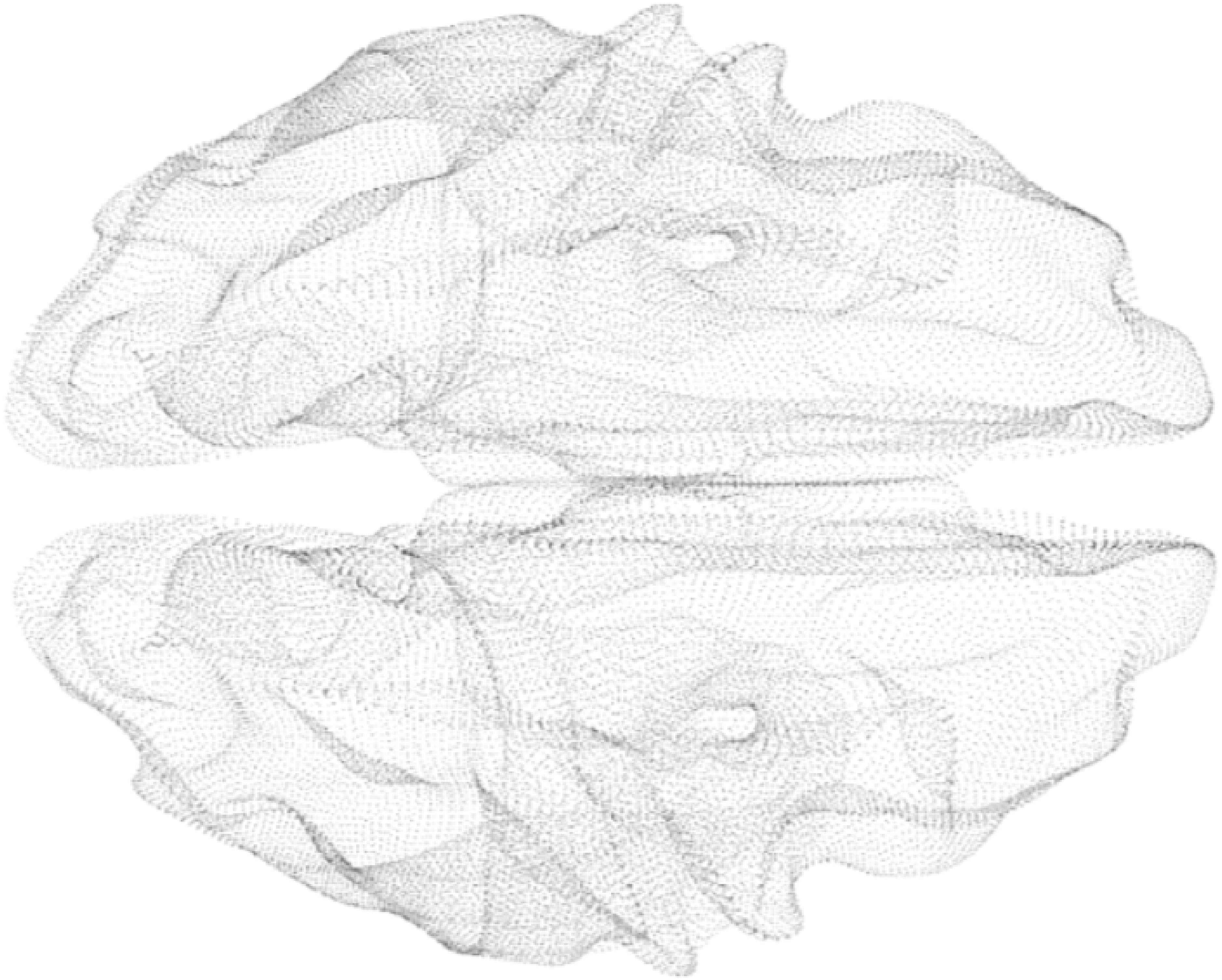
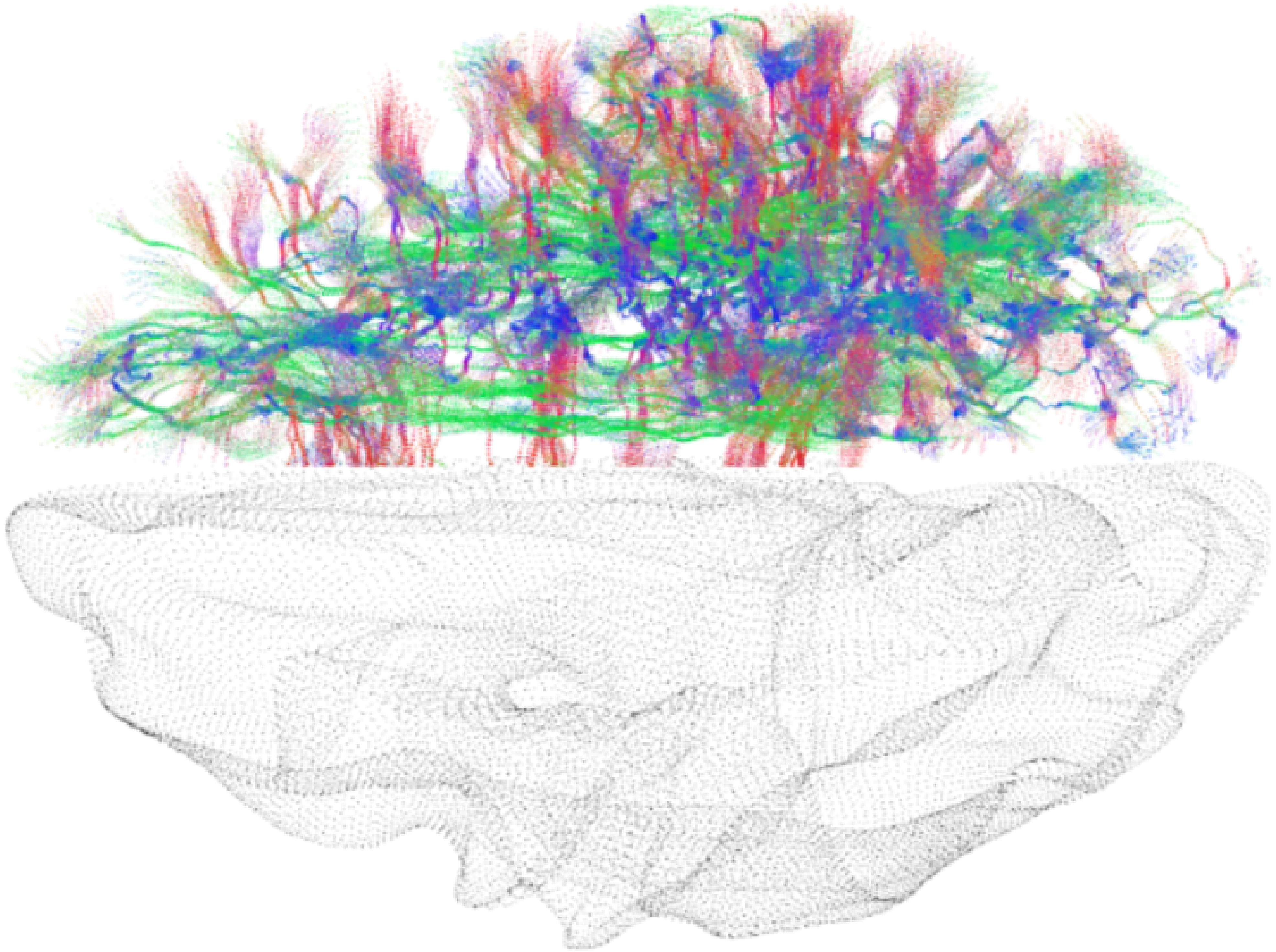
→ Map high-resolution connectomes (at the granularity of voxels or vertices)



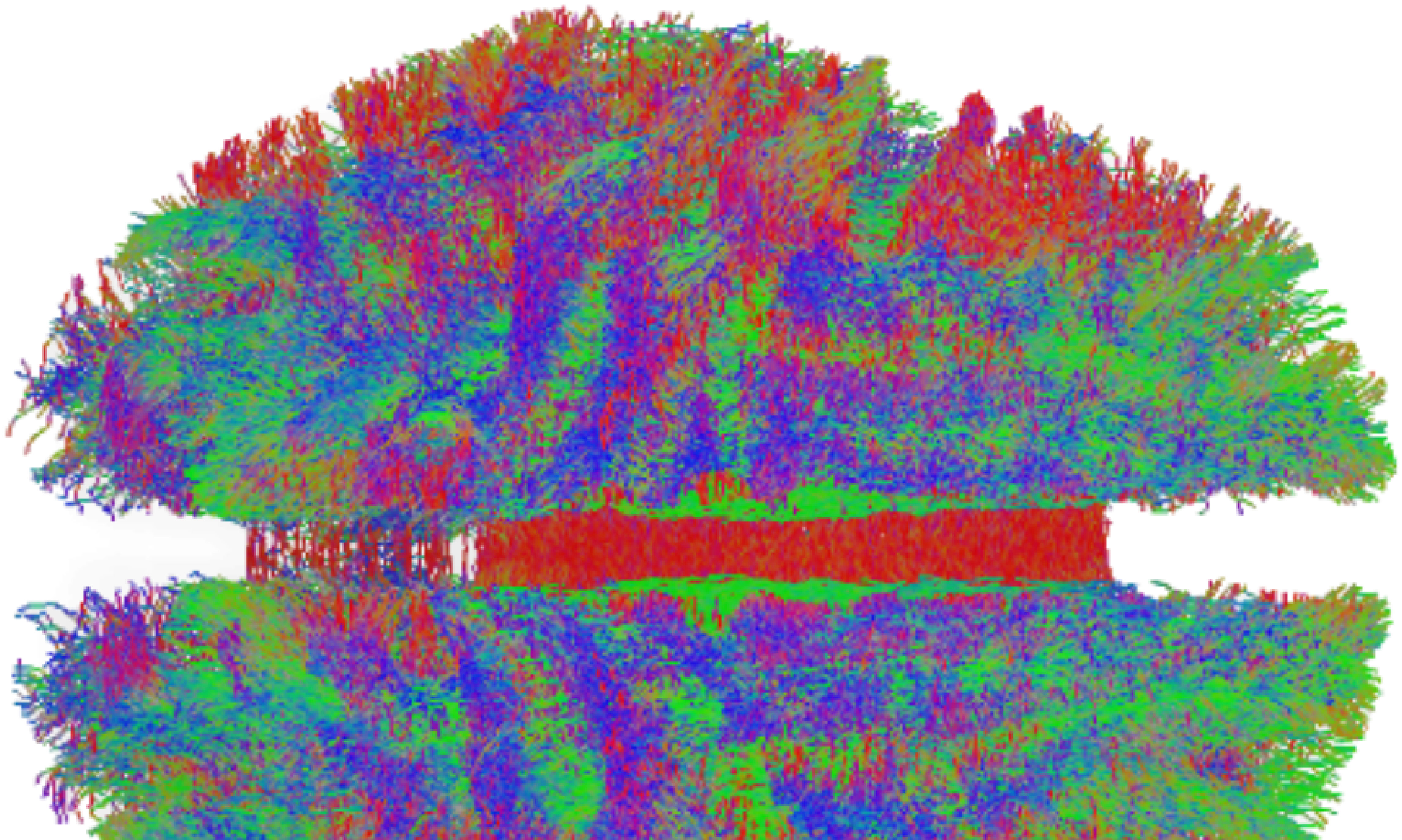


High-resolution connectome eigenmodes

Perform tractography over a large sample (e.g. HCP YA)

Map high-resolution connectomes (at the granularity of voxels or vertices)

→ Group-average connectome; shared anatomical connectivity backbone



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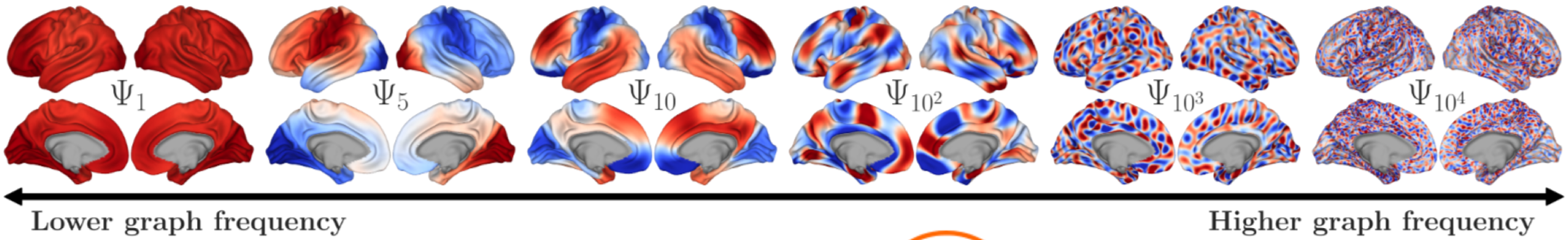
Perform tractography over a large sample (e.g. HCP YA)

Map high-resolution connectomes (at the granularity of voxels or vertices)

Group-average connectome; shared anatomical connectivity backbone

→ Perform GSP; map graph Laplacian eigenmodes as an information basis



Signal ← $X = \sum_i \alpha_i \psi_i + \varepsilon = \hat{X} + \varepsilon$ Reconstruction

Signal reconstruction via eigenmodes:

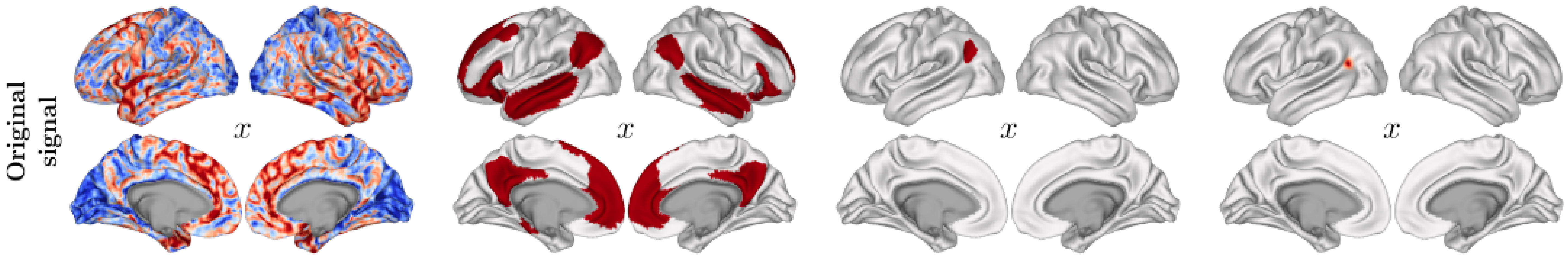
Signal

$$X = \sum_i \alpha_i \psi_i + \varepsilon = \hat{X} + \varepsilon$$

Reconstruction

Signal reconstruction via eigenmodes:

Signal $\leftarrow X = \sum_i \alpha_i \psi_i + \varepsilon = \hat{X} + \varepsilon \rightarrow$ Reconstruction



Signal reconstruction via eigenmodes:

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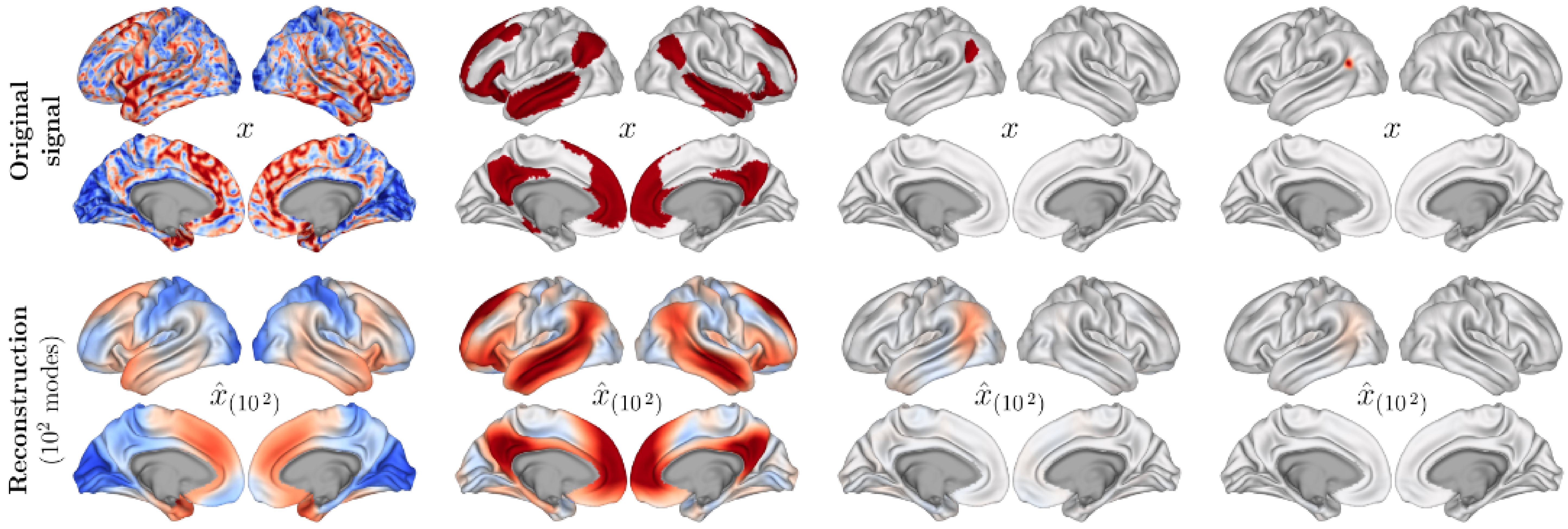

Signal reconstruction via eigenmodes:

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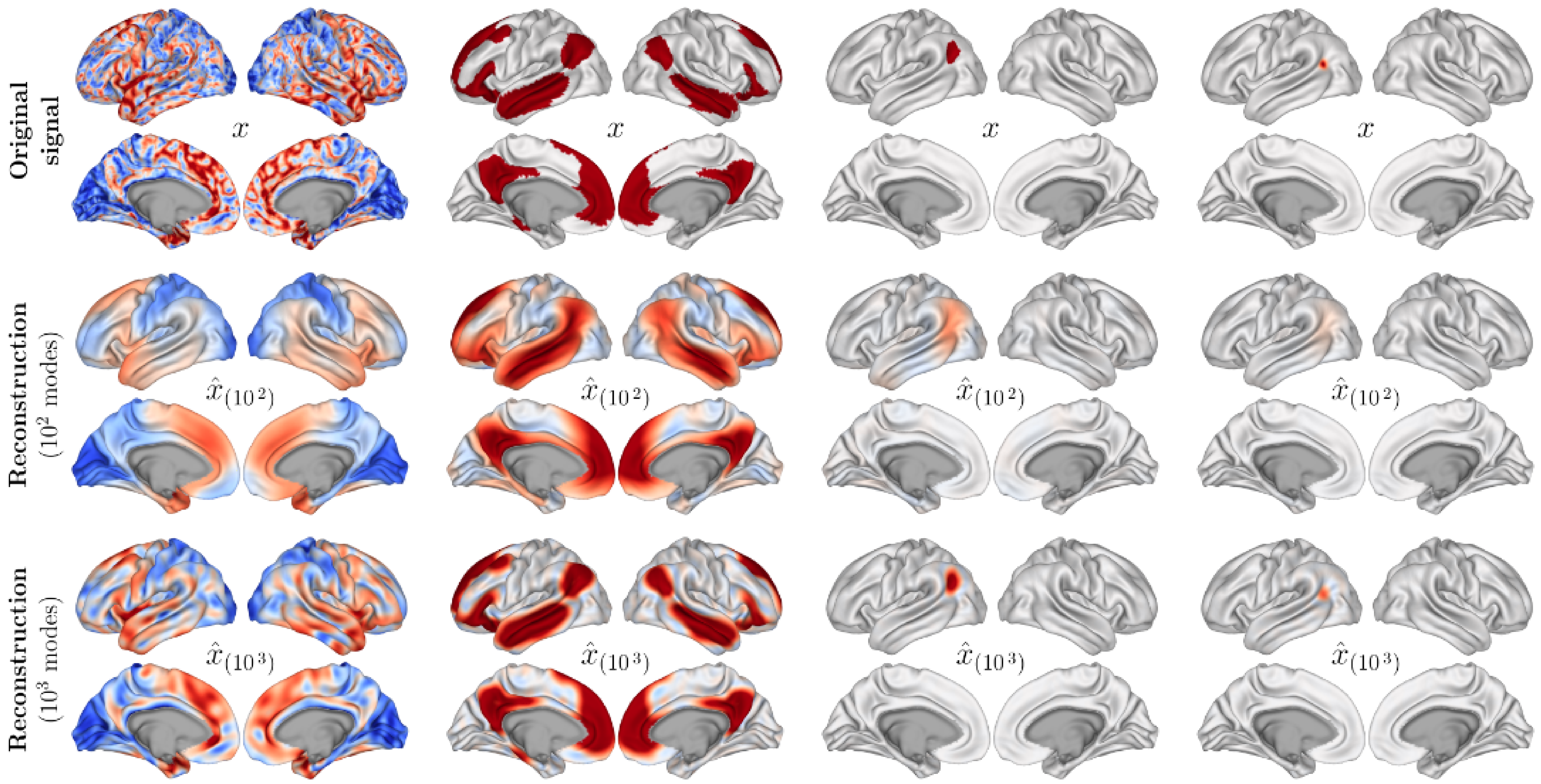
Reconstruction



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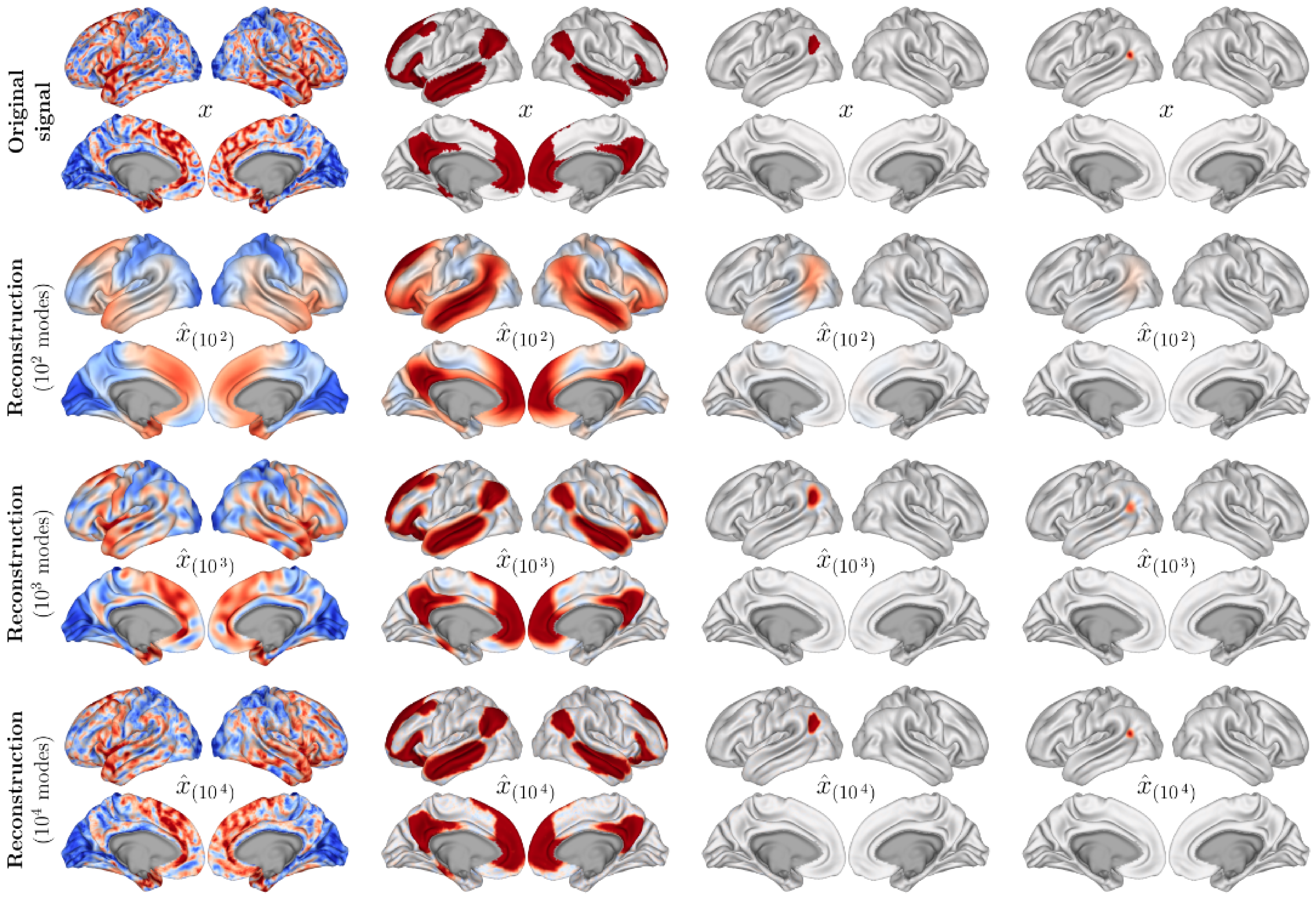
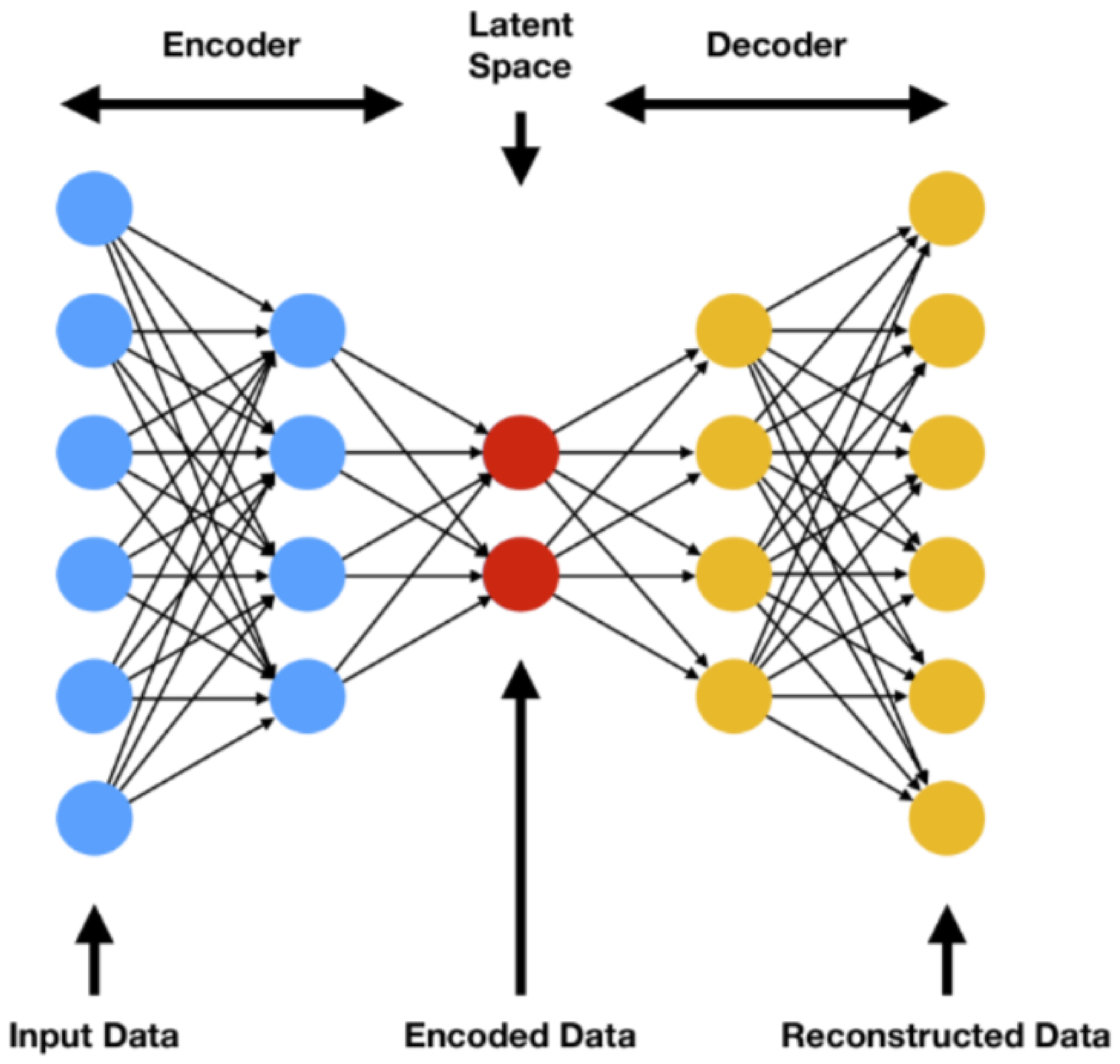


Conceptual analogy with autoencoders:



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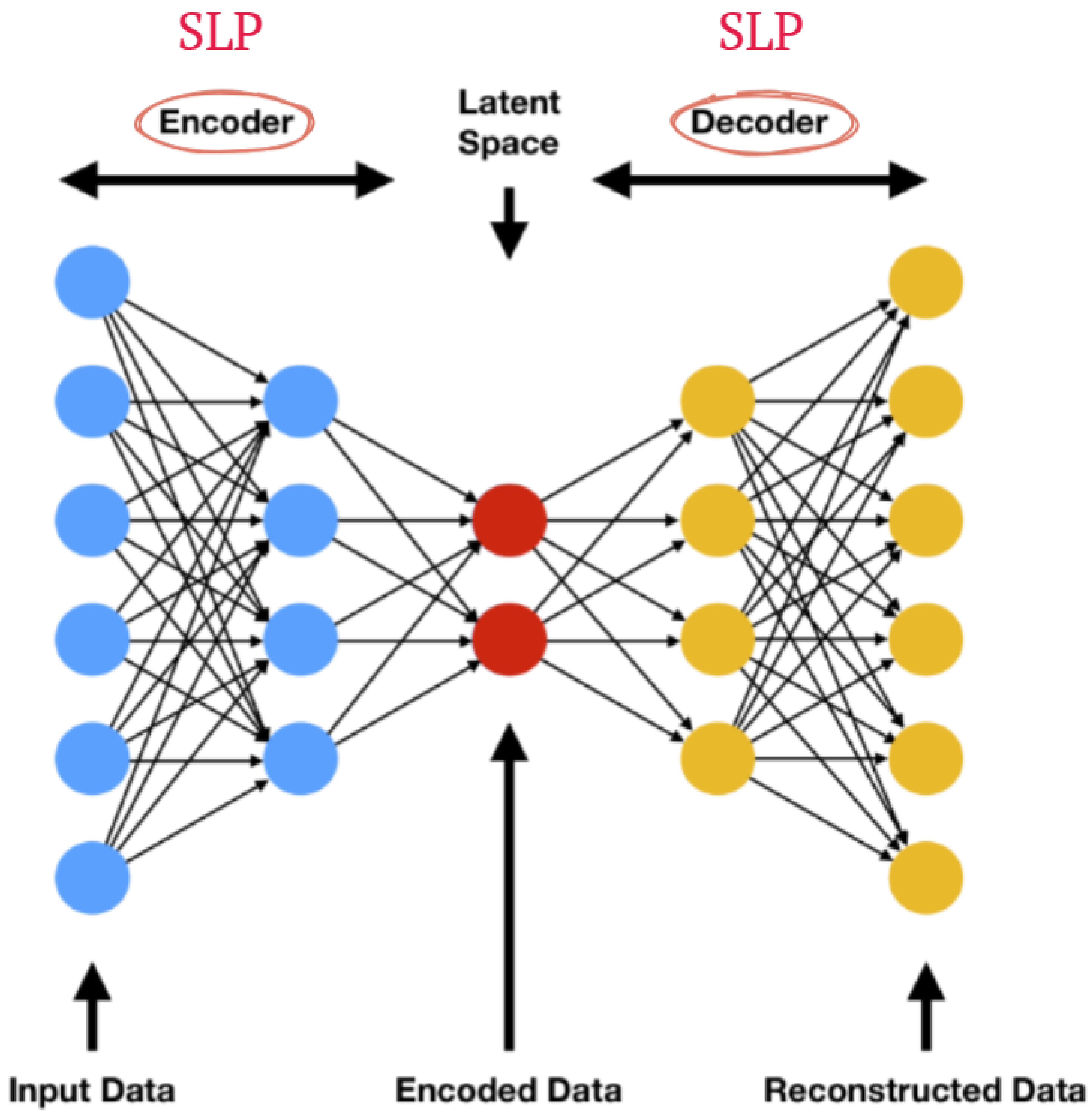

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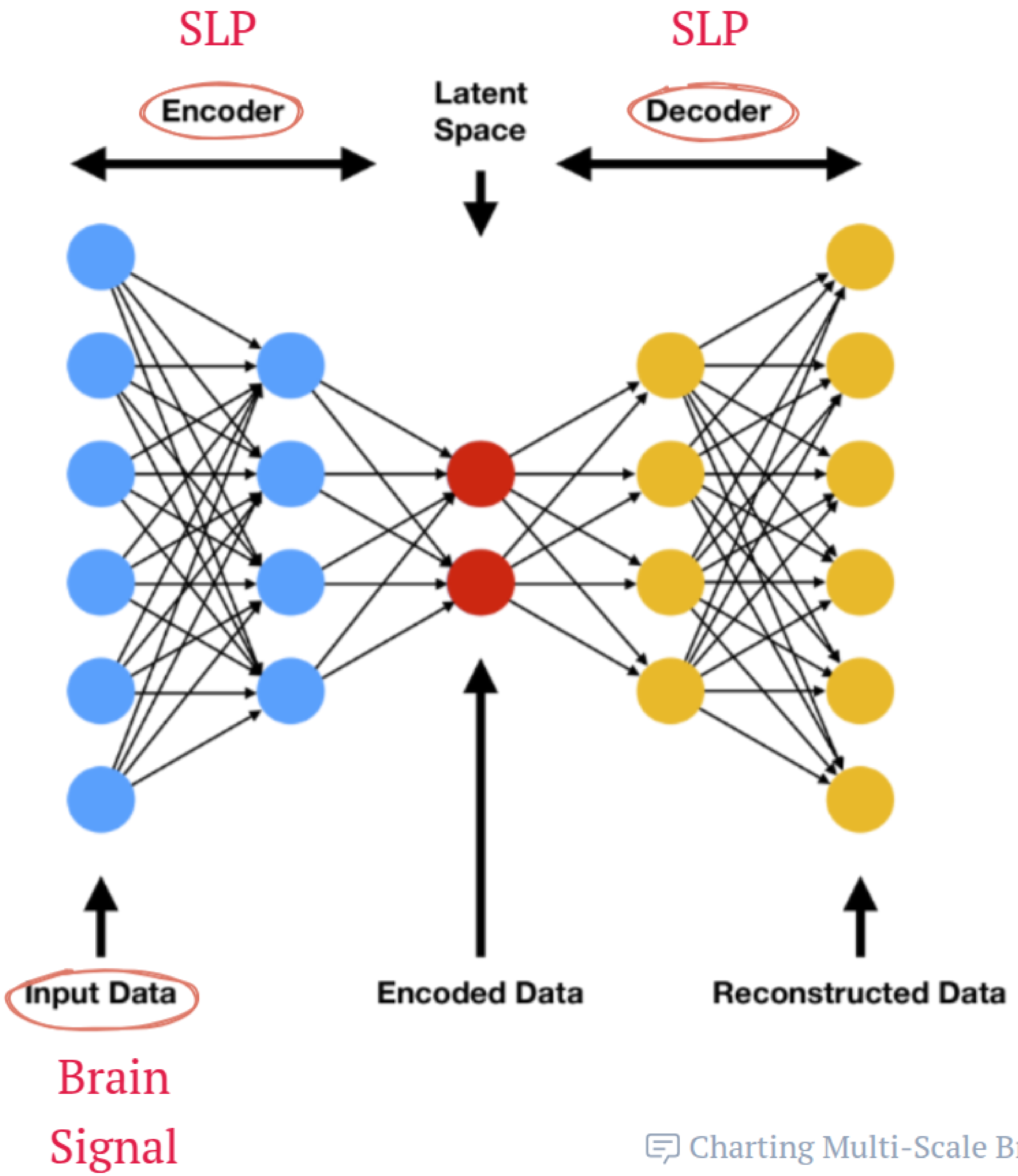

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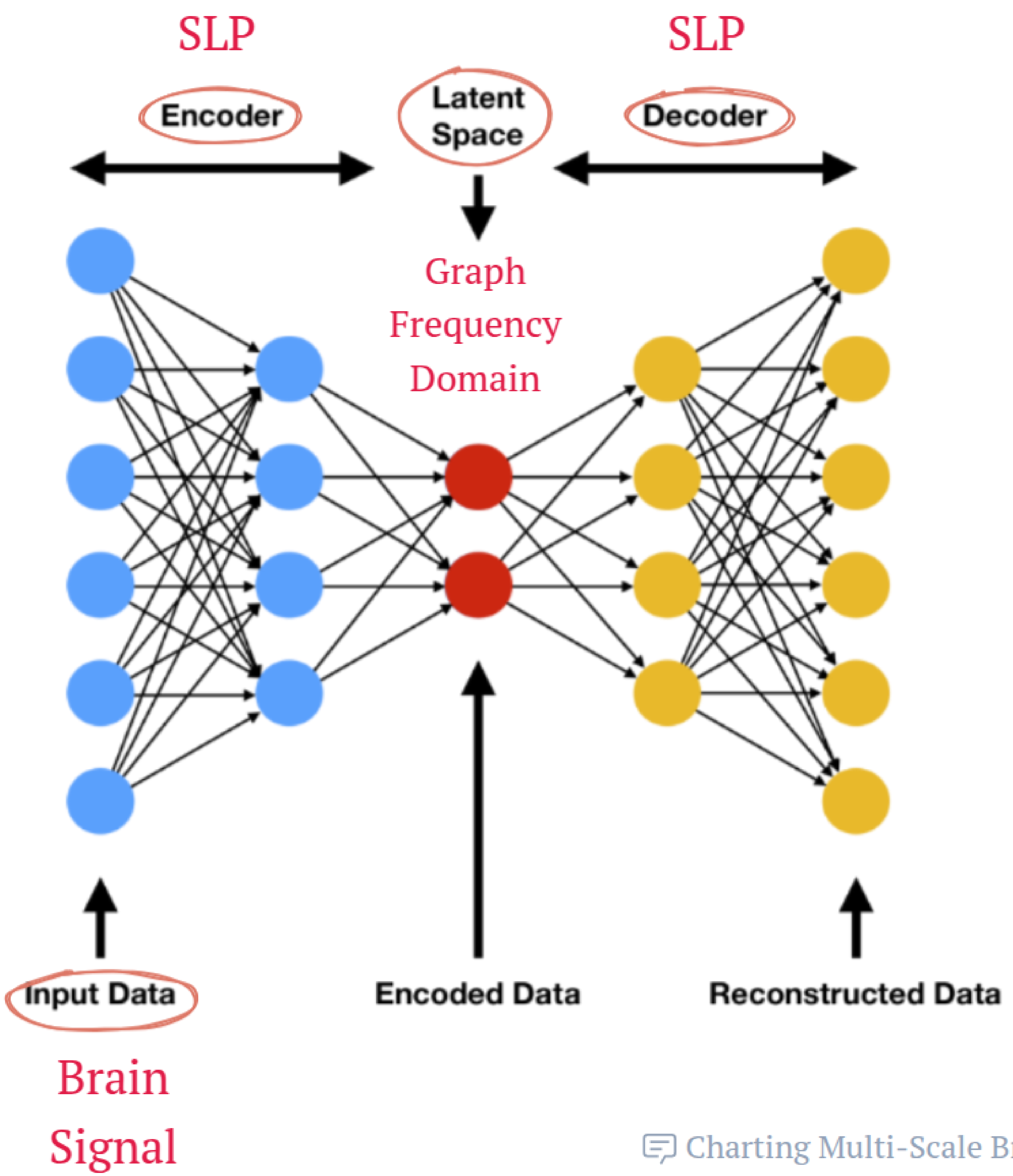

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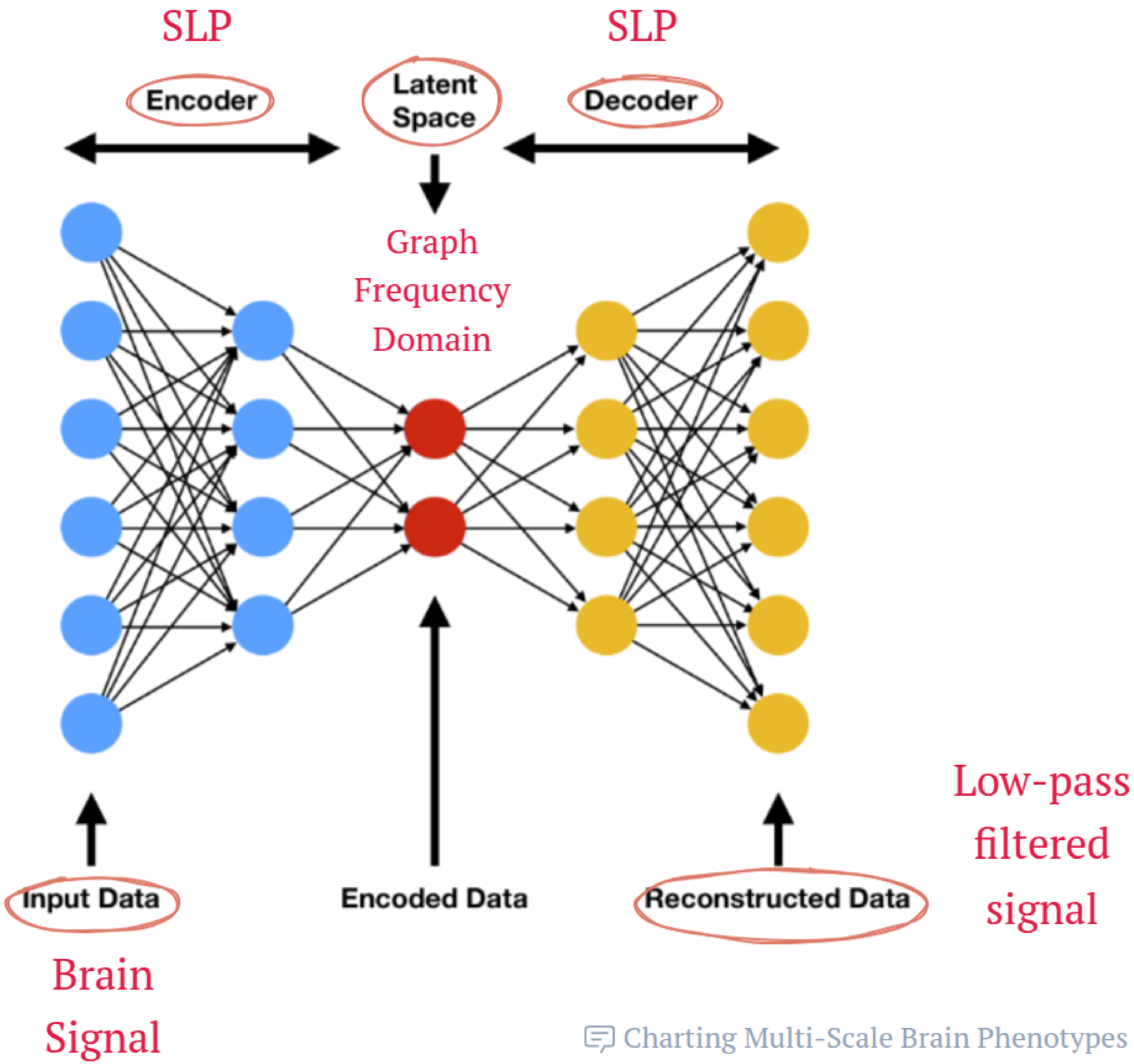
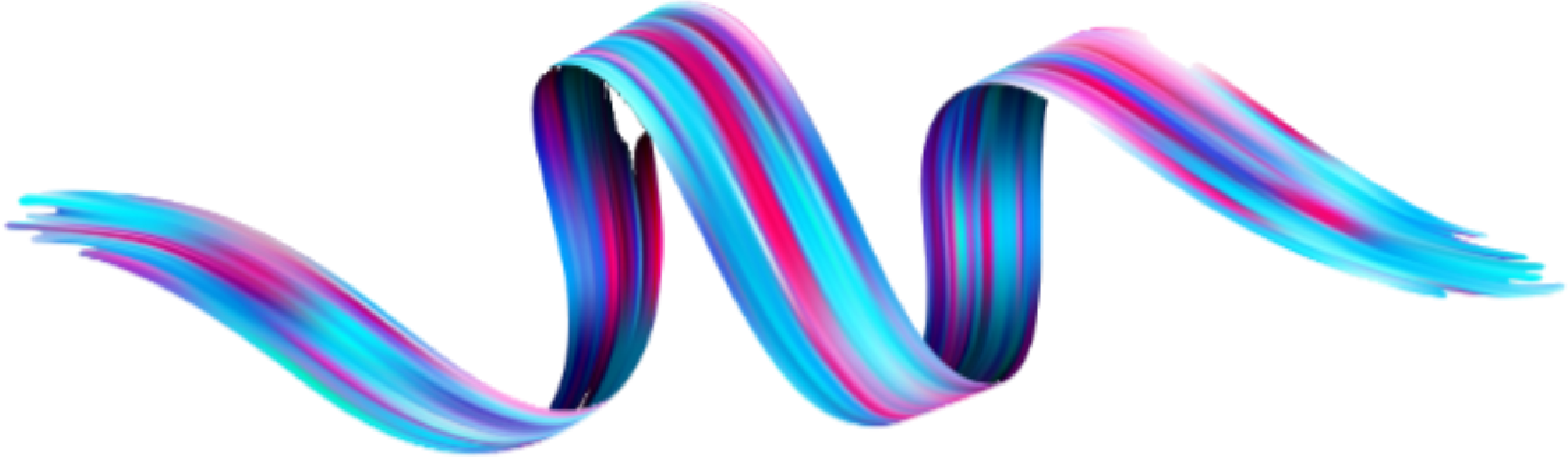


Spectral Normative Modeling

Spectral Normative Modeling

SNM

Bain Eigenmodes

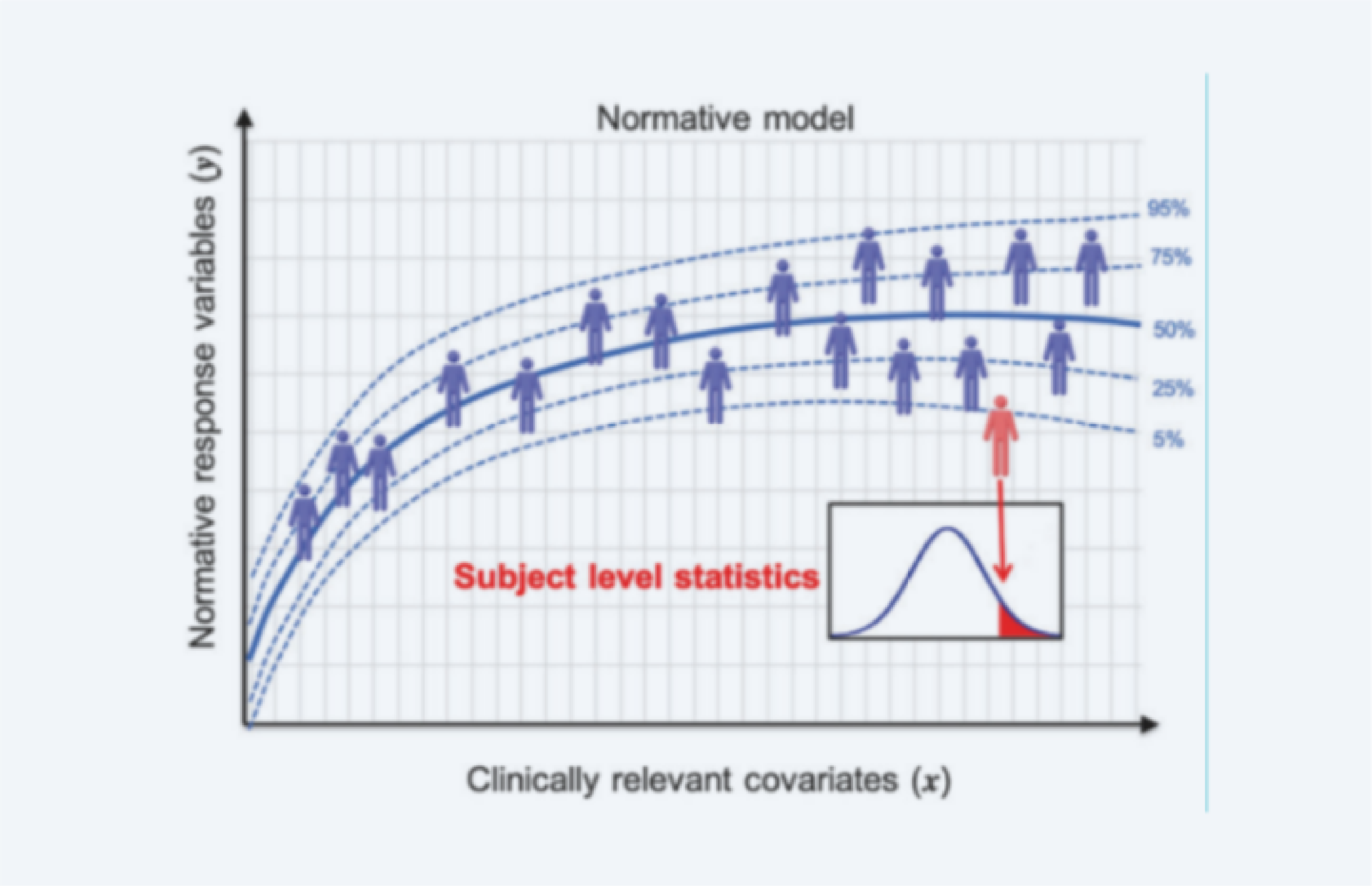


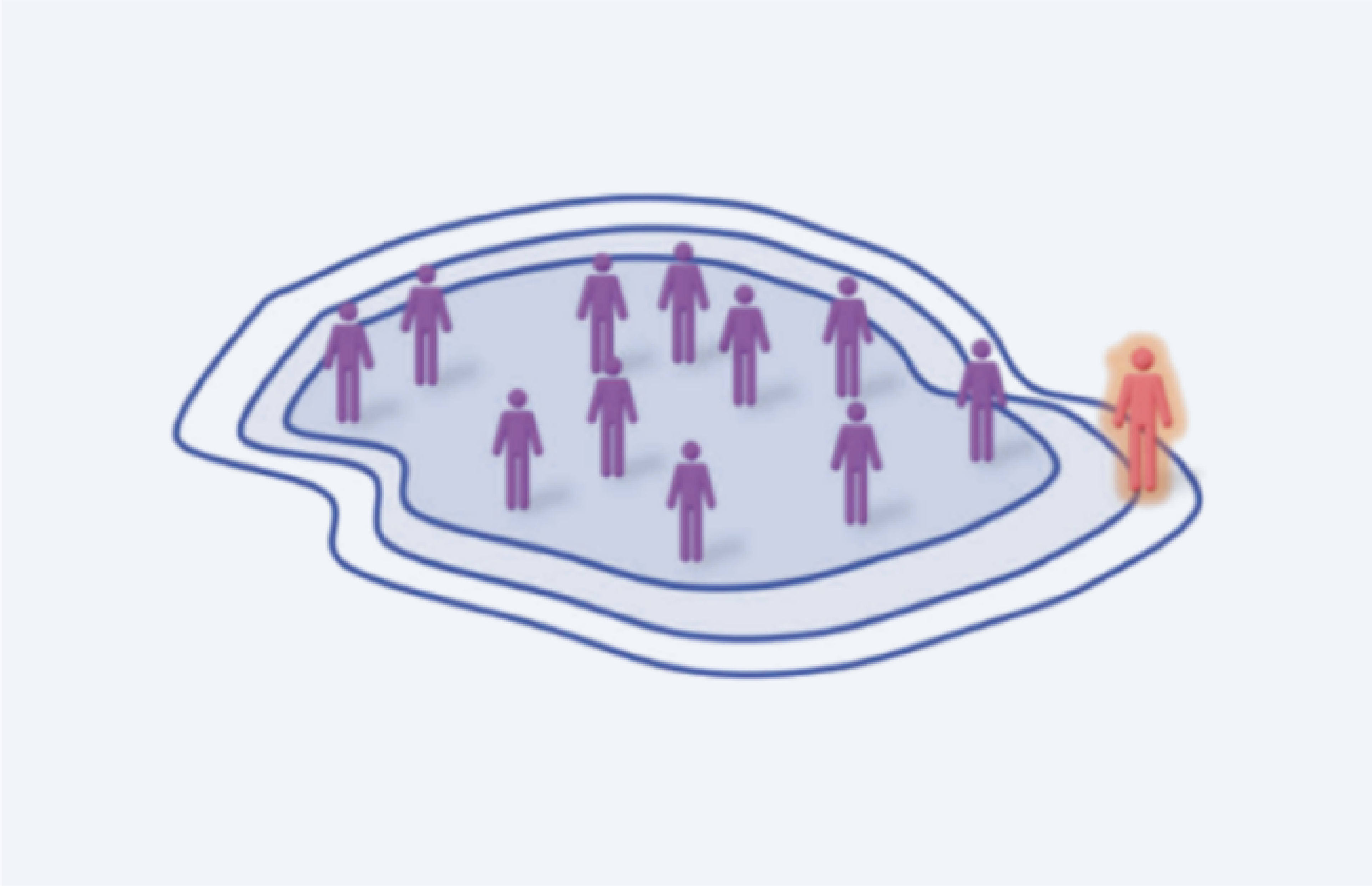
Normative Modeling

Normative Modeling

Normative Modeling

→ Characterizes population-level phenotype distribution to detect individual deviations from the norm.

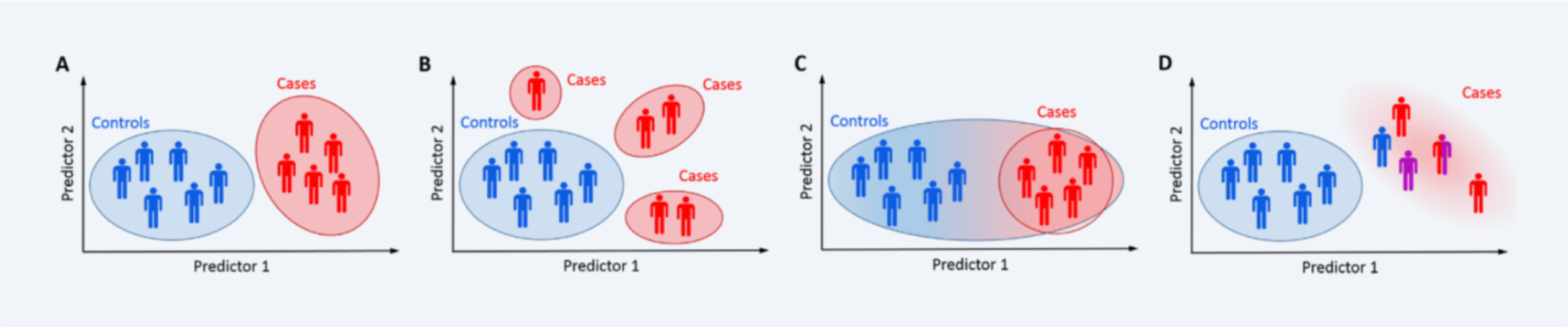




Marquand et al. (2019)

Normative Modeling & Personalized Medicine

→ Enables exploration of individual-level differences and heterogeneity of pathological deviations.



Marquand et al. (2016)

Conventional Normative Models (Direct Models)

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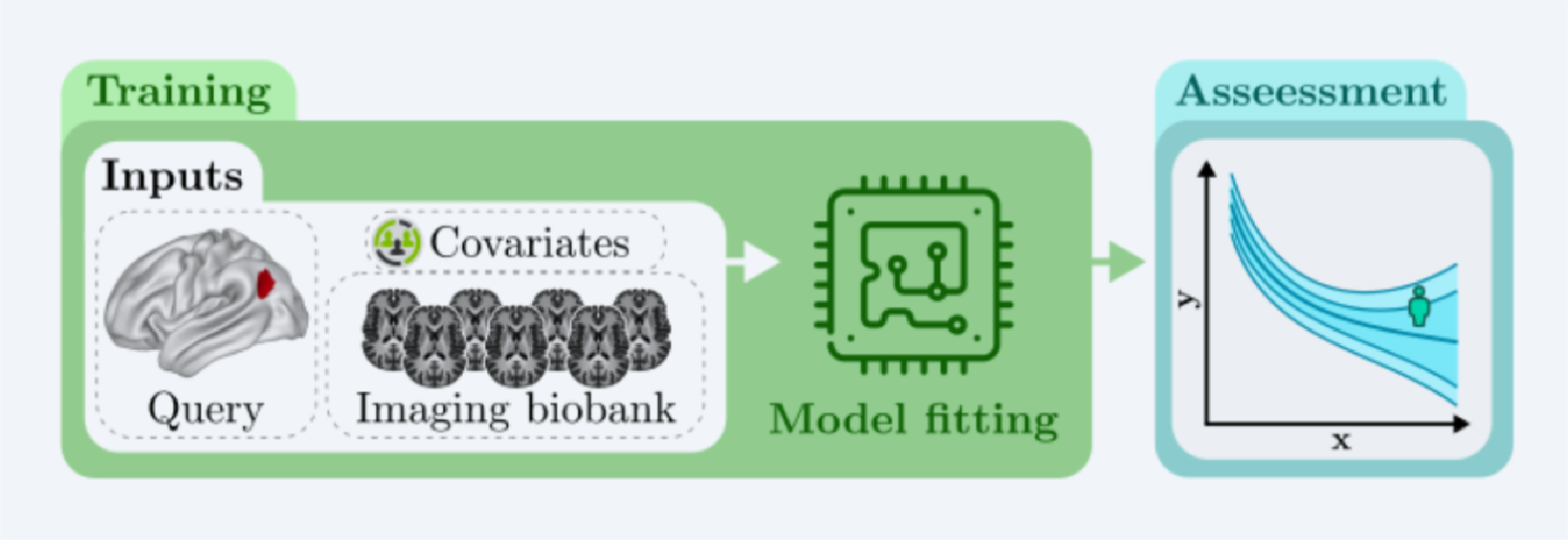
→ Trained to infer normative ranges of a **predefined fixed phenotype (y)** from a set of covariates (X).

$$y \sim N(\mu, \sigma^2),\ \mu = f_1(x_1) + f_2(x_2) + \ldots + f_n(x_n)$$

Dinga et al. (2021)

Conventional Normative Models (Direct Models)

Trained to infer normative ranges of a **predefined fixed phenotype (y)** from a set of covariates (X).



Mansour L. et al. (2025)

Spectral Normative Modeling (SNM)

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→ **Idea:** Use GSP as means to compress and reconstruct normative ranges.

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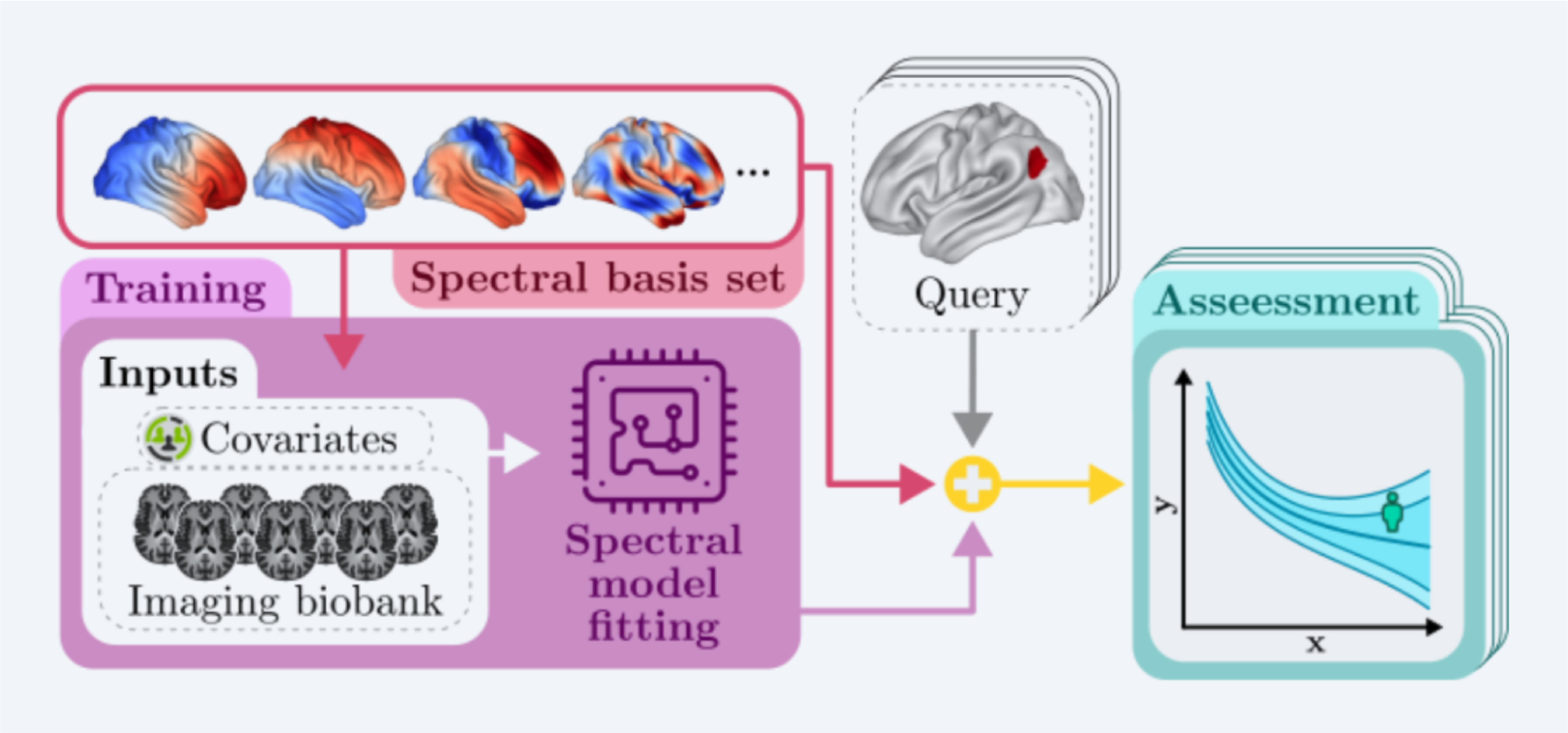


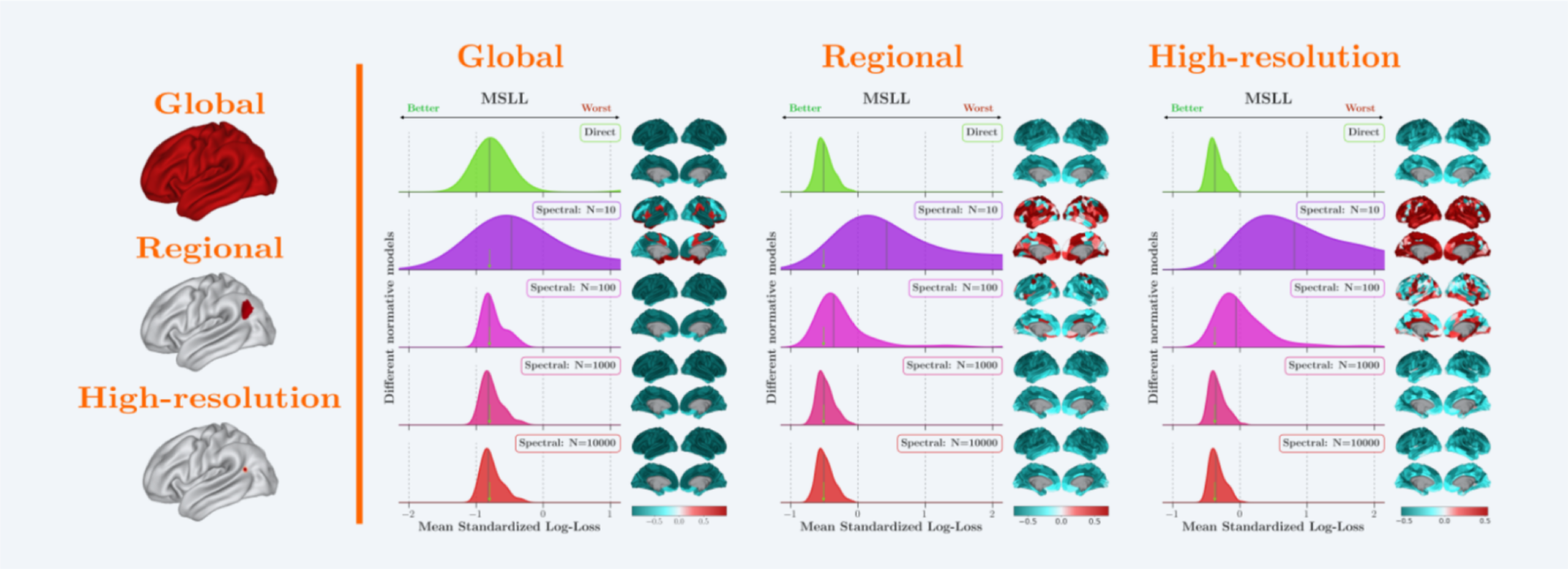
Mansour L. et al. (2025)

Charting Multi-Scale Brain Phenotypes Using Spectral Normative Models

SNM performance

SNM performance

→ With at least **1000 modes** SNM achieves comparable estimates to that of a direct model.

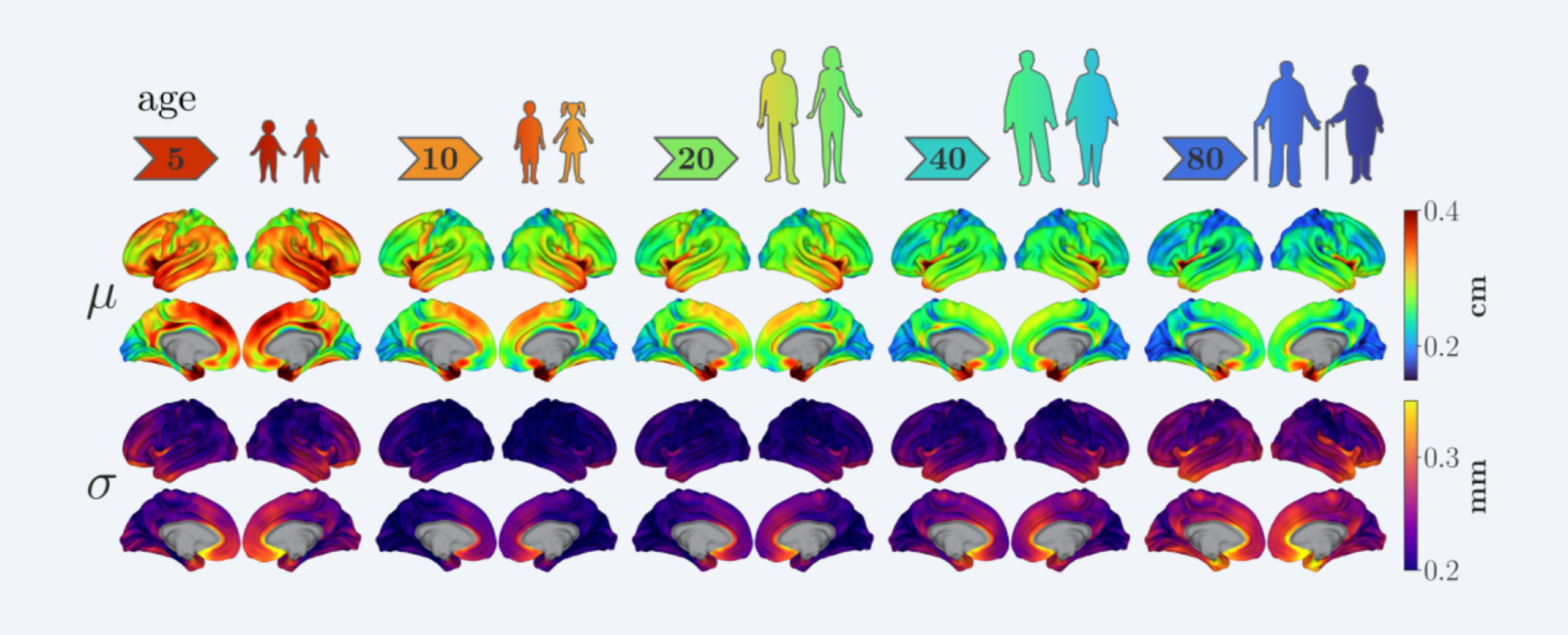


Charting Multi-Scale Brain Phenotypes Using Spectral Normative Models

High-resolution normative modeling

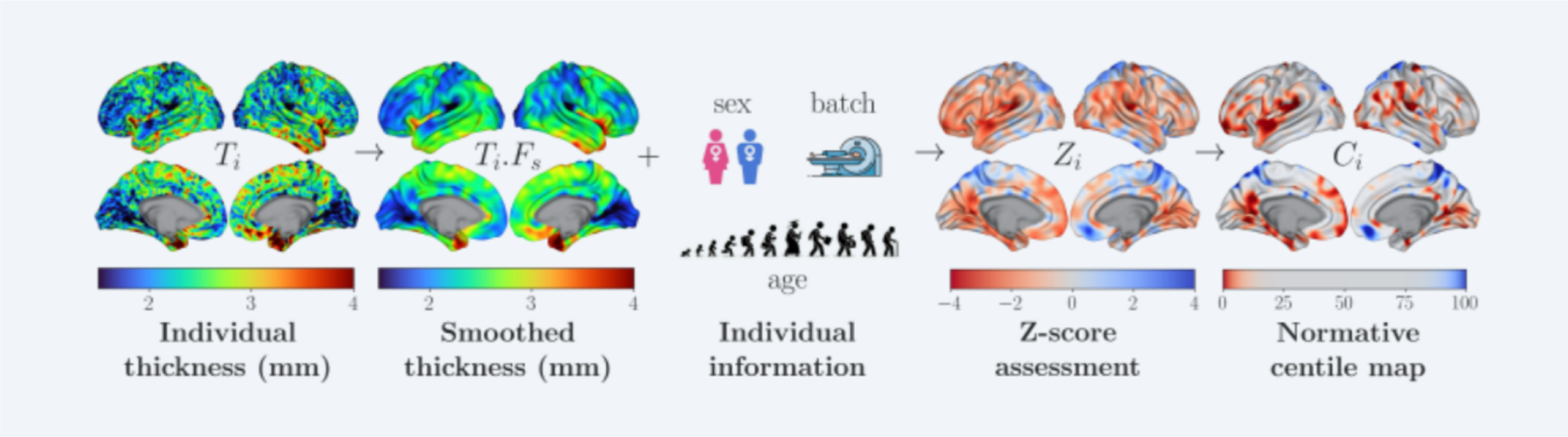
High-resolution normative modeling

→ Efficiently estimate charts at **vertex-resolution** across human lifespan.



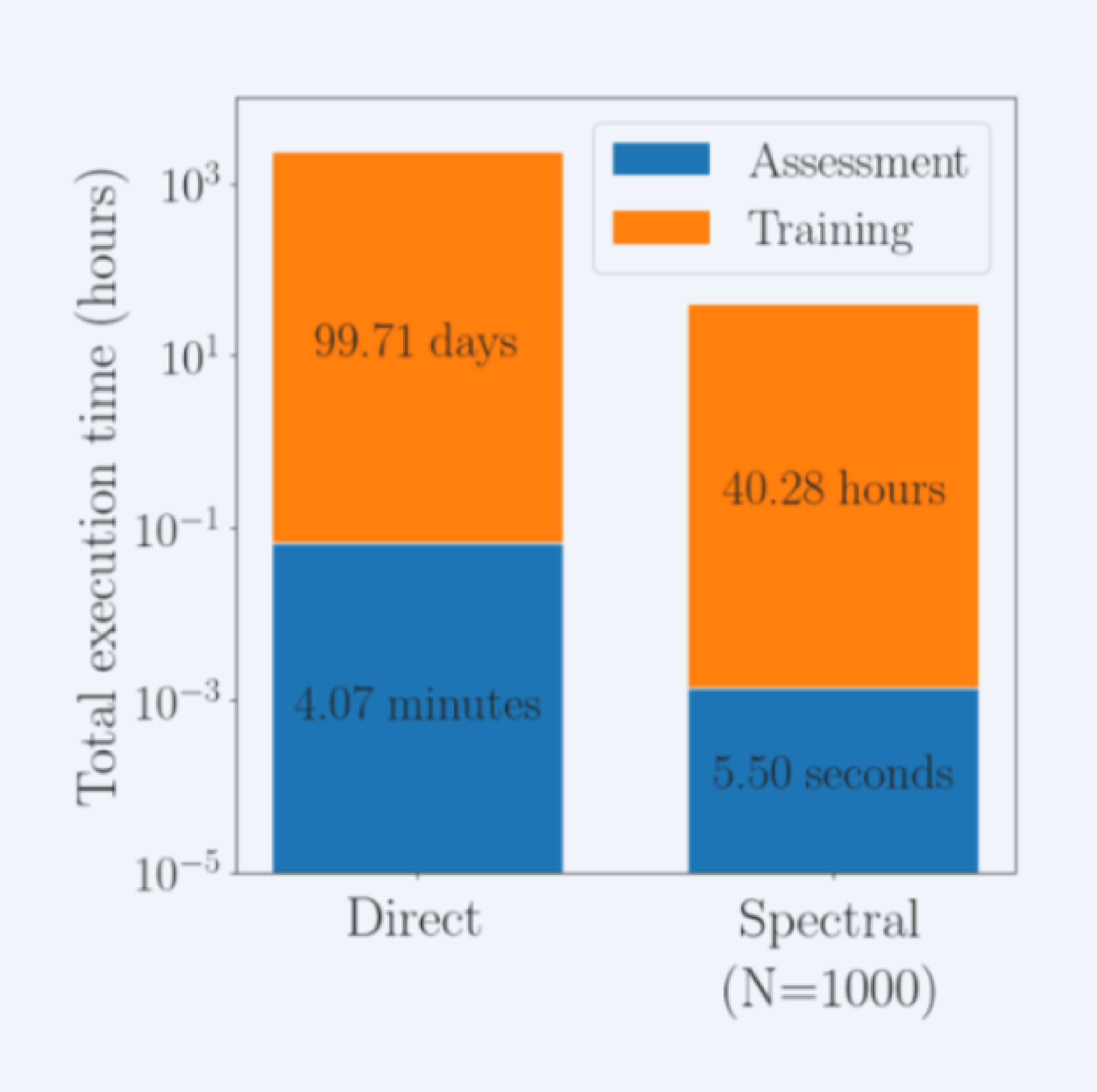
High-resolution normative modeling

→ Enables derivation of **individualized** vertex-resolution abnormality scores.



High-resolution normative modeling

→ For vertex-resolution NMs, SNM achieves **100x to 10,000x** speedup.



Clinical application: AD dementia

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→ Train SNM on a healthy normative sample (HCP Lifespan)

Clinical application: AD dementia

Train SNM on a healthy normative sample (HCP Lifespan)

→ Transfer learning: freeze demography covariates, fine-tune site effects (harmonization)

$$\mu_y = f_\mu(age,\ sex,\ batch) = \boxed{w_\mu \Phi(age) + \alpha_\mu(sex)} + \boxed{\beta_\mu(batch)} + \epsilon_\mu$$

$$\sigma_y = f_\sigma^+(age,\ sex,\ batch) = \boxed{w_\sigma^+ \Phi(age) + \alpha_\sigma^+(sex)} + \boxed{\beta_\sigma^+(batch)} + \epsilon_\sigma$$

Clinical application: AD dementia

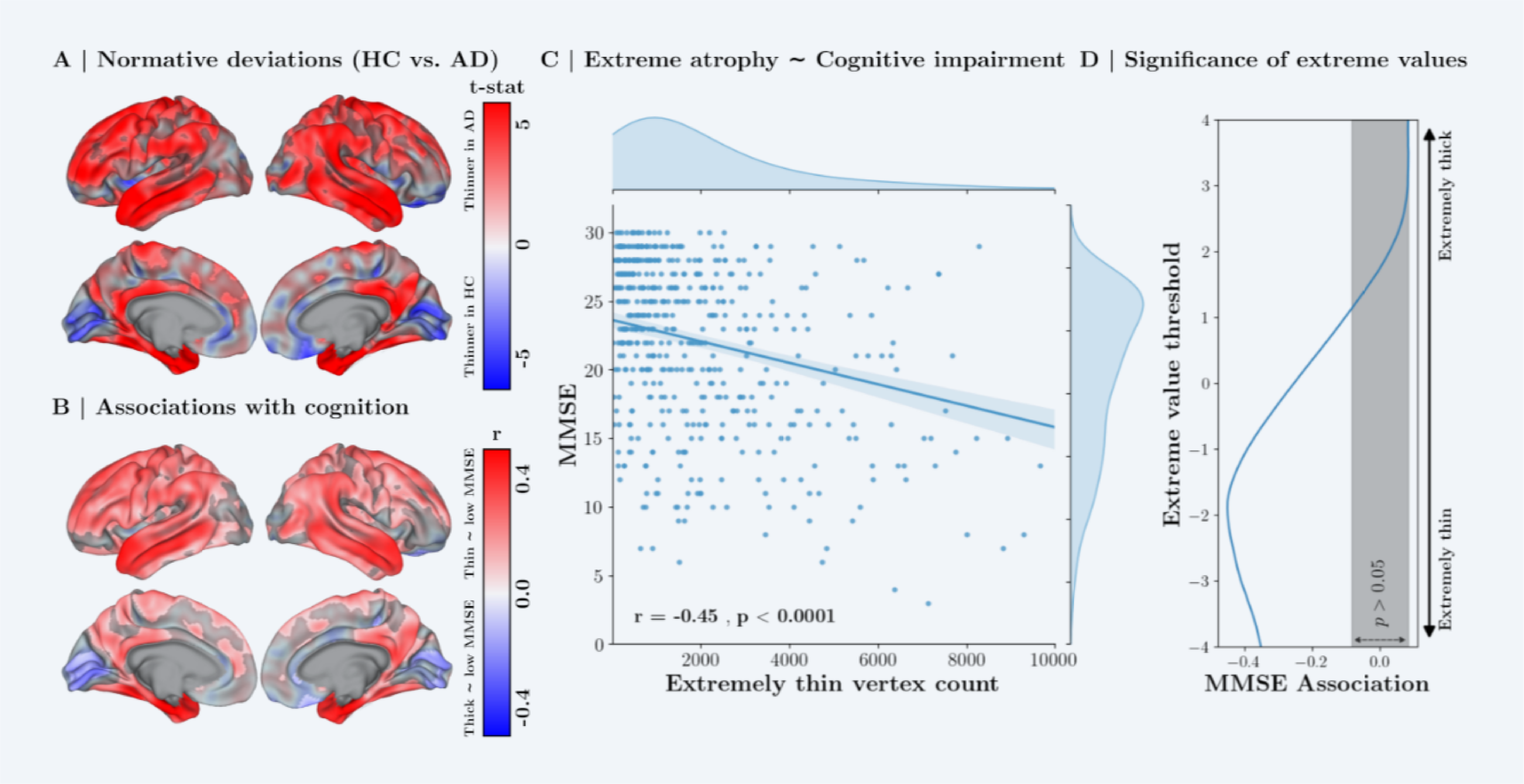
Train SNM on a healthy normative sample (HCP Lifespan)

Transfer learning: freeze demography covariates, fine-tune site effects (harmonization)

→ Clinical data: Healthy Controls (HC), Mild Cognitive Impairment (MCI), & Alzheimer's Disease (AD)

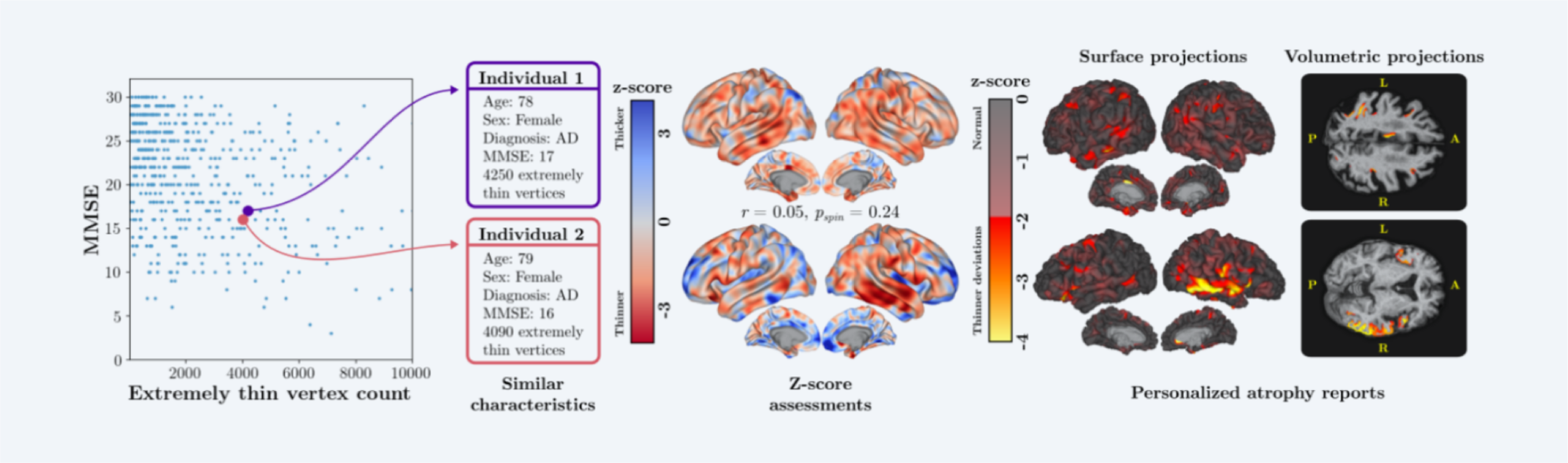
Clinical application: AD dementia

→ Population-level evaluations: Cortical correlates of cognitive decline



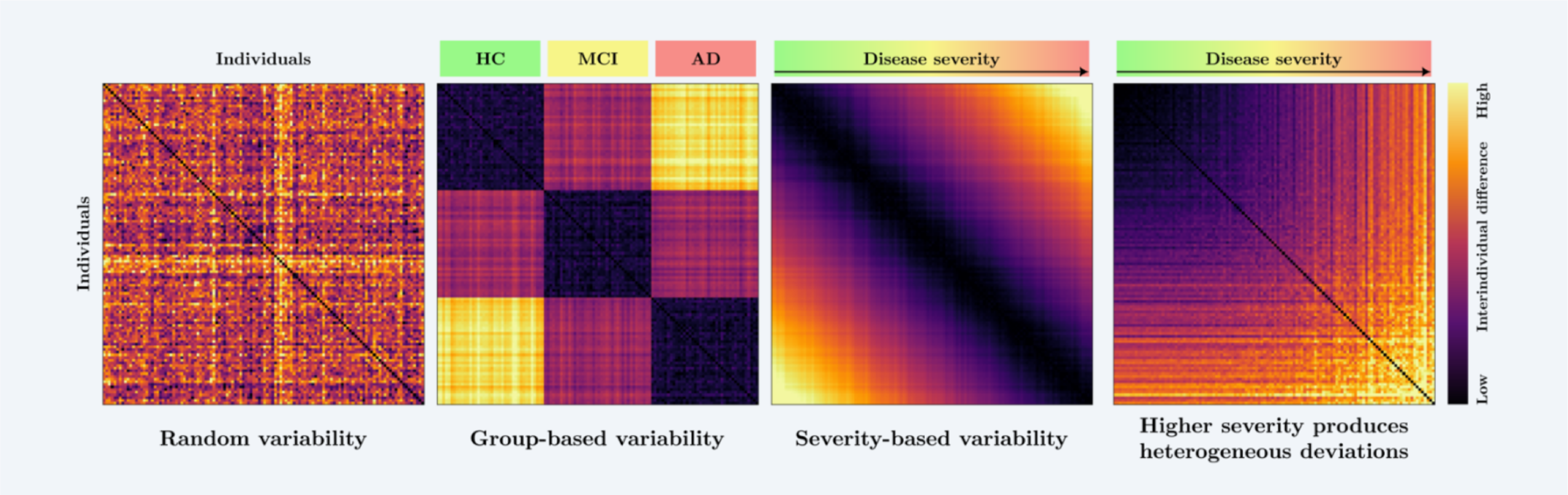
Clinical application: AD dementia

→ Individual-level evaluations: Heterogeneous landscape of dementia-induced cortical atrophy



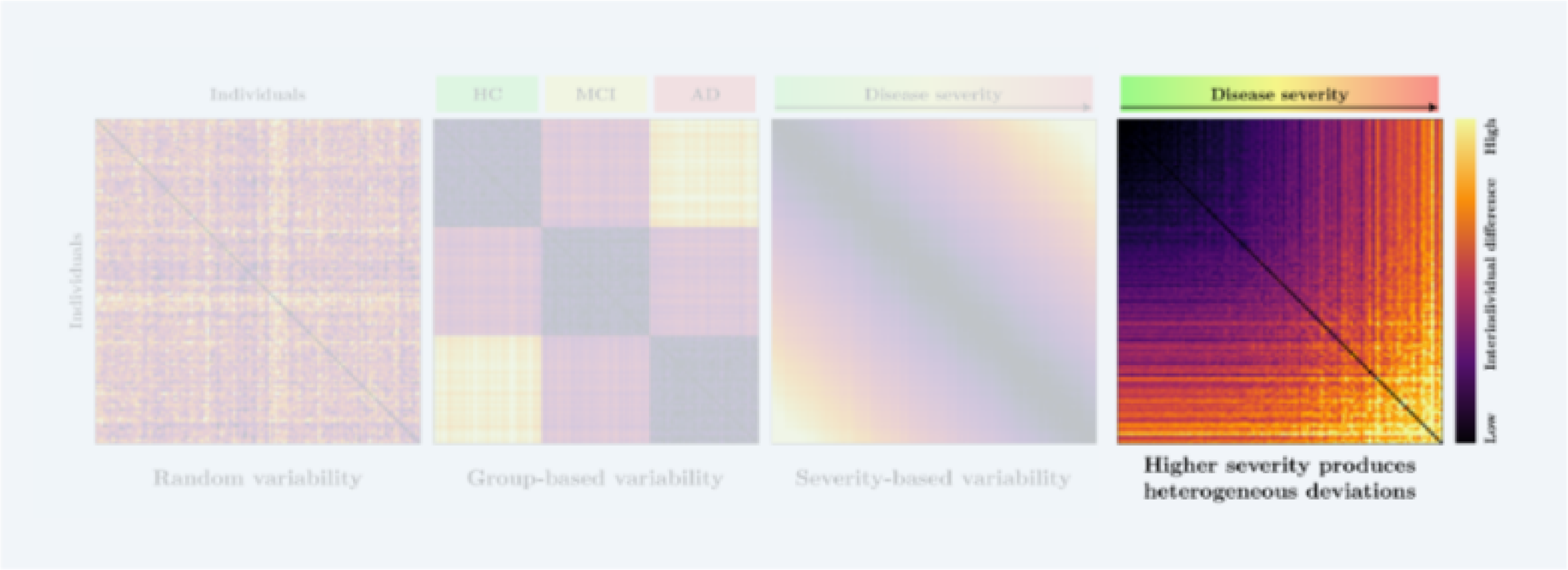
Clinical application: AD dementia

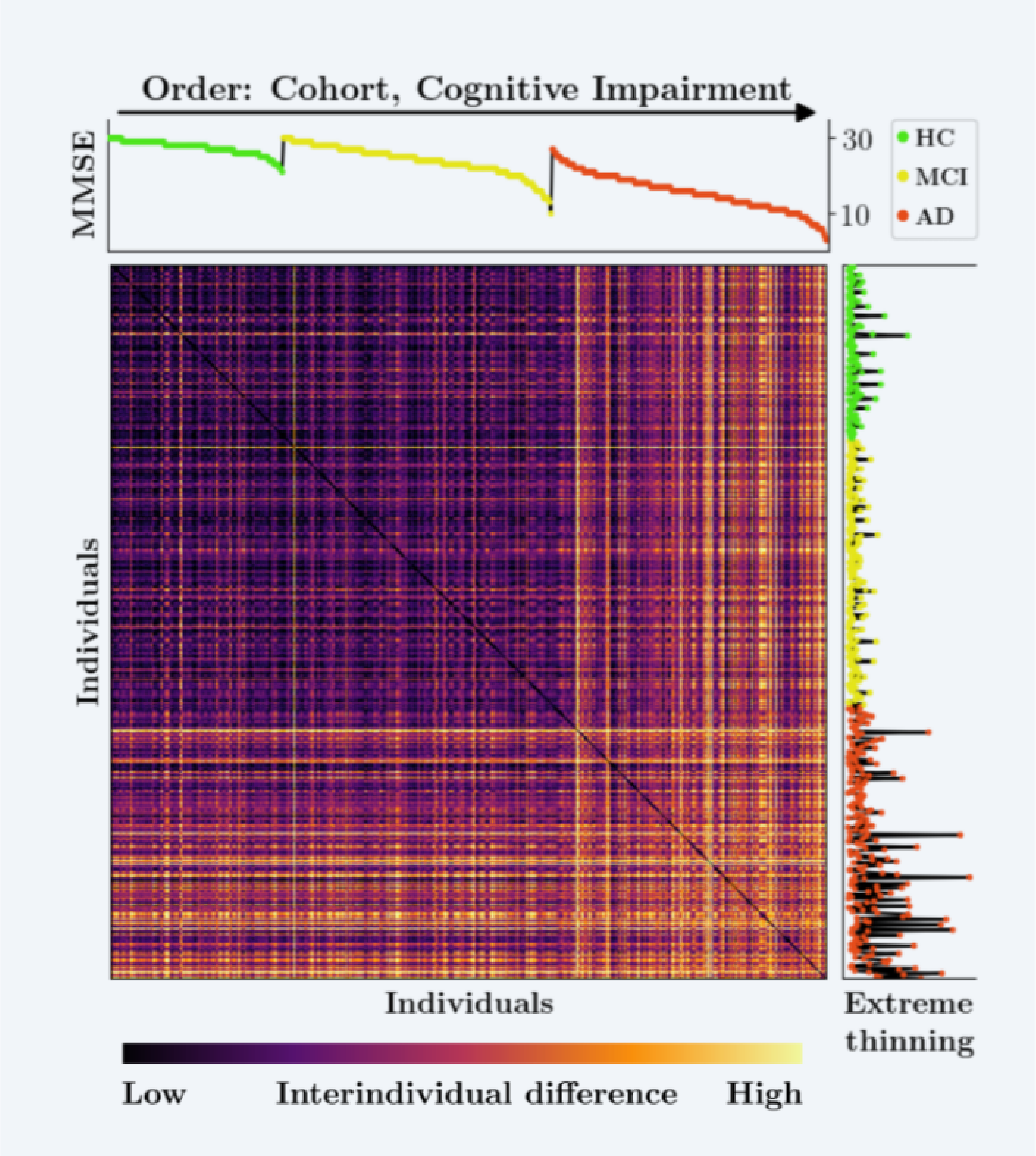
→ Hypothetical patterns of interindividual variability



Clinical application: AD dementia

→ Empirical variability

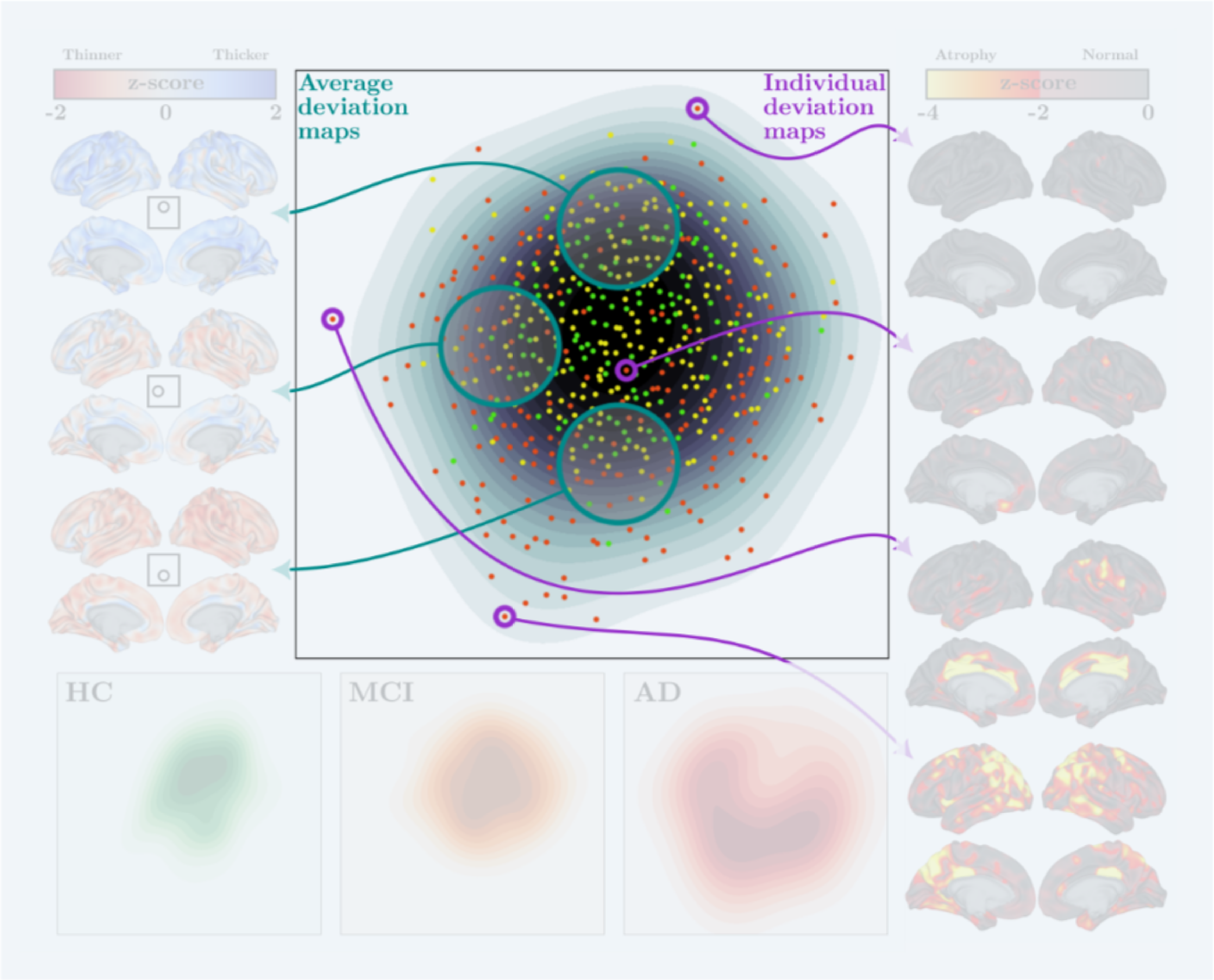




Charting Multi-Scale Brain Phenotypes Using Spectral Normative Models

Clinical application: AD dementia

→ Individual heterogeneity



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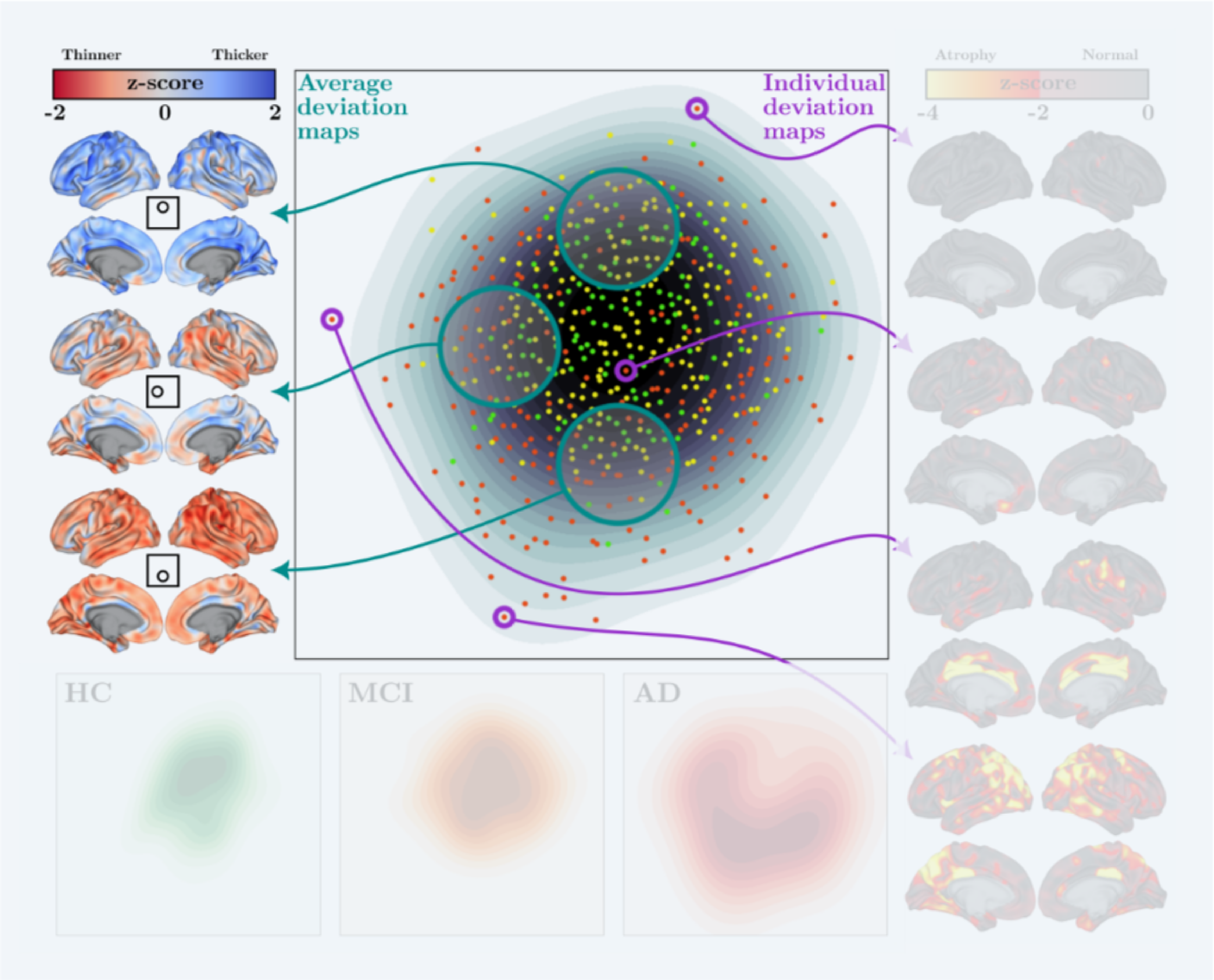

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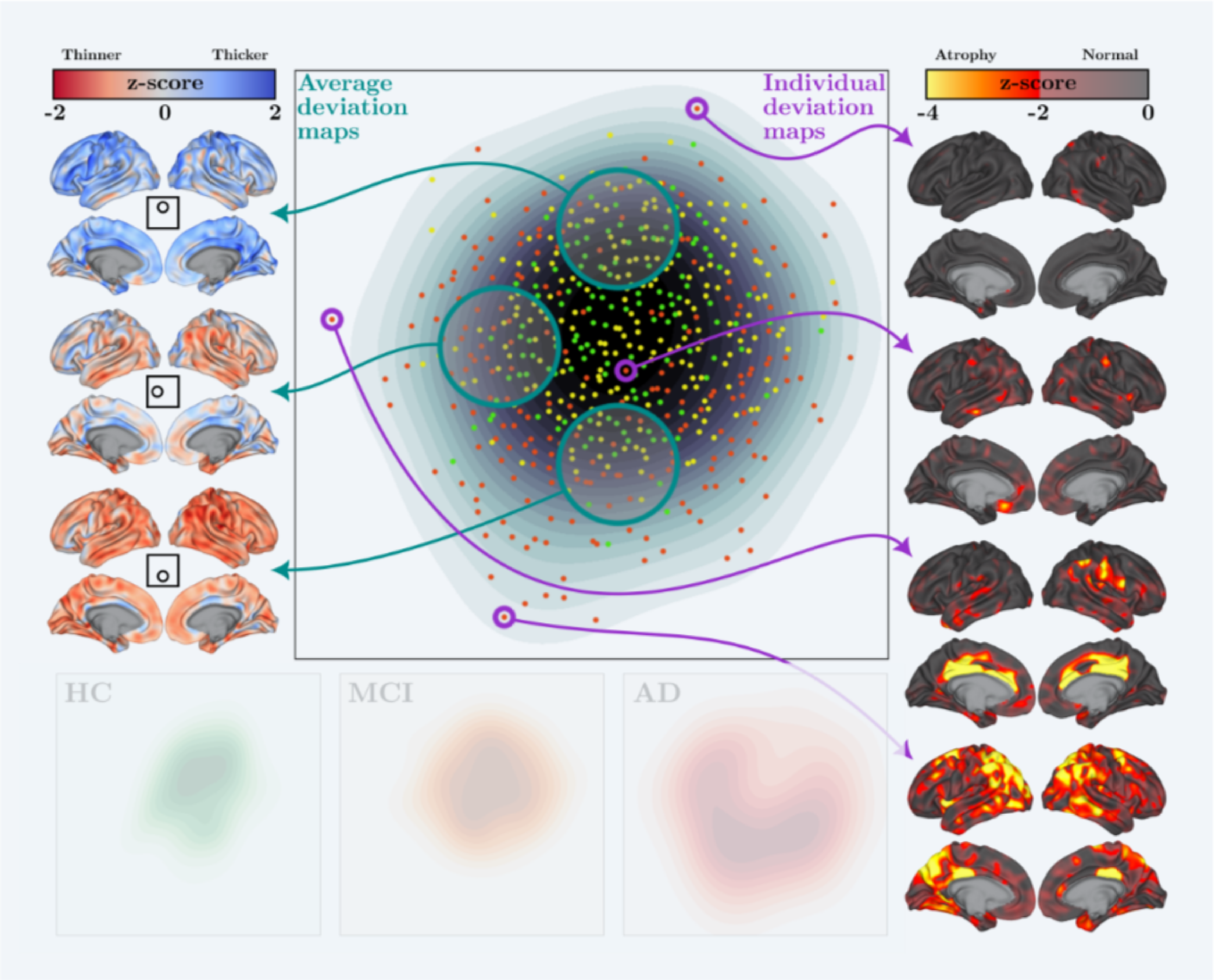

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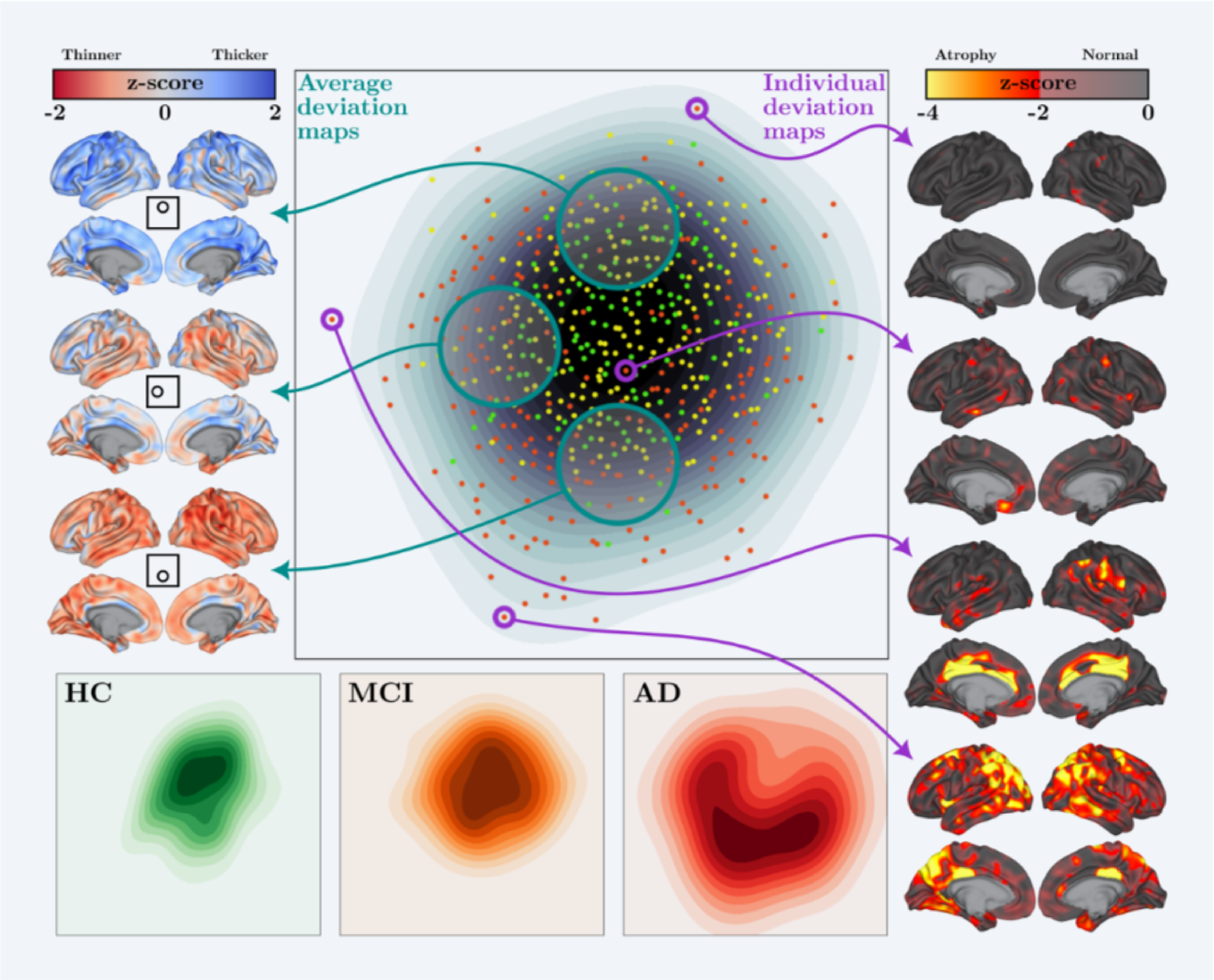

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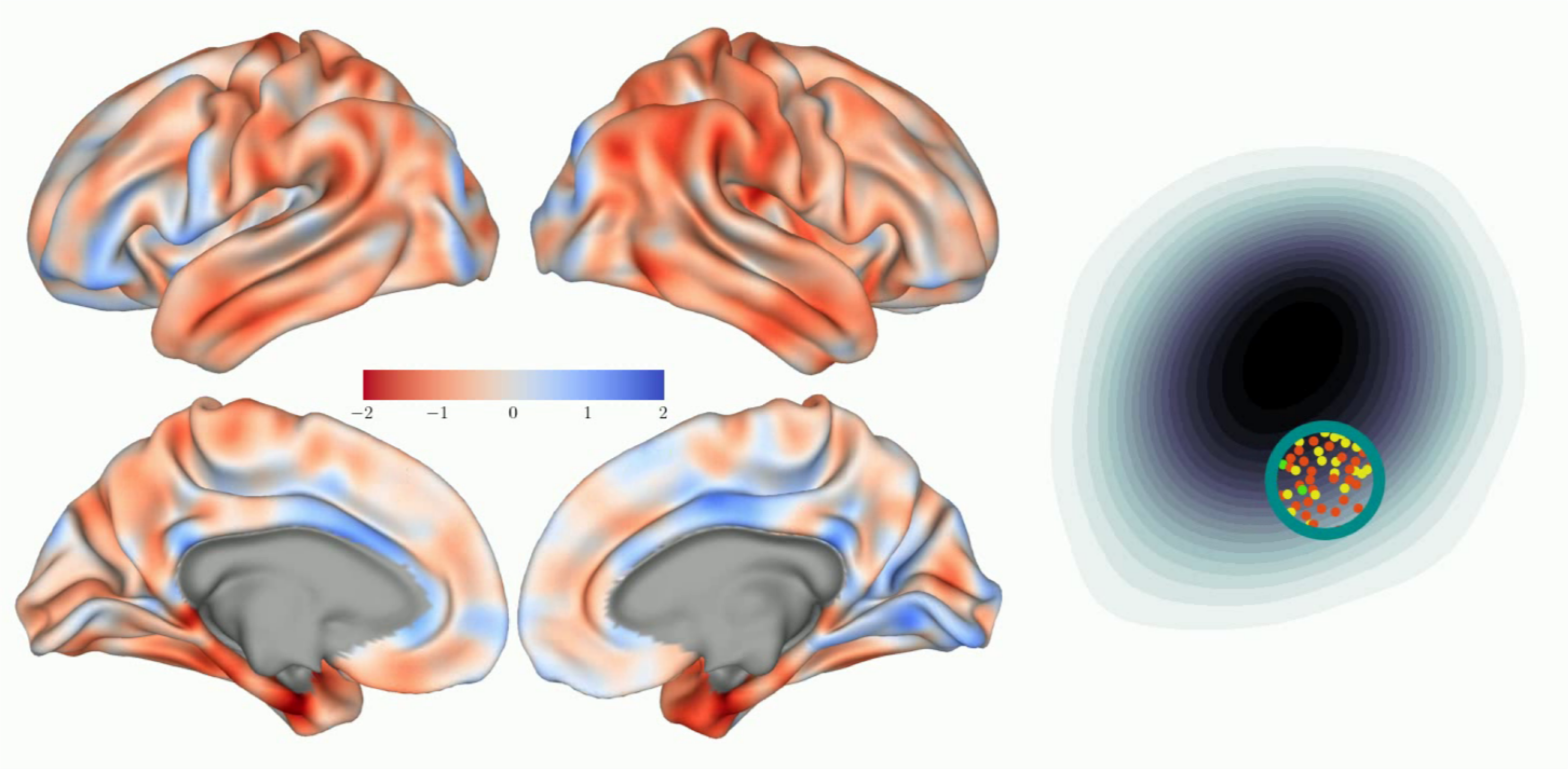

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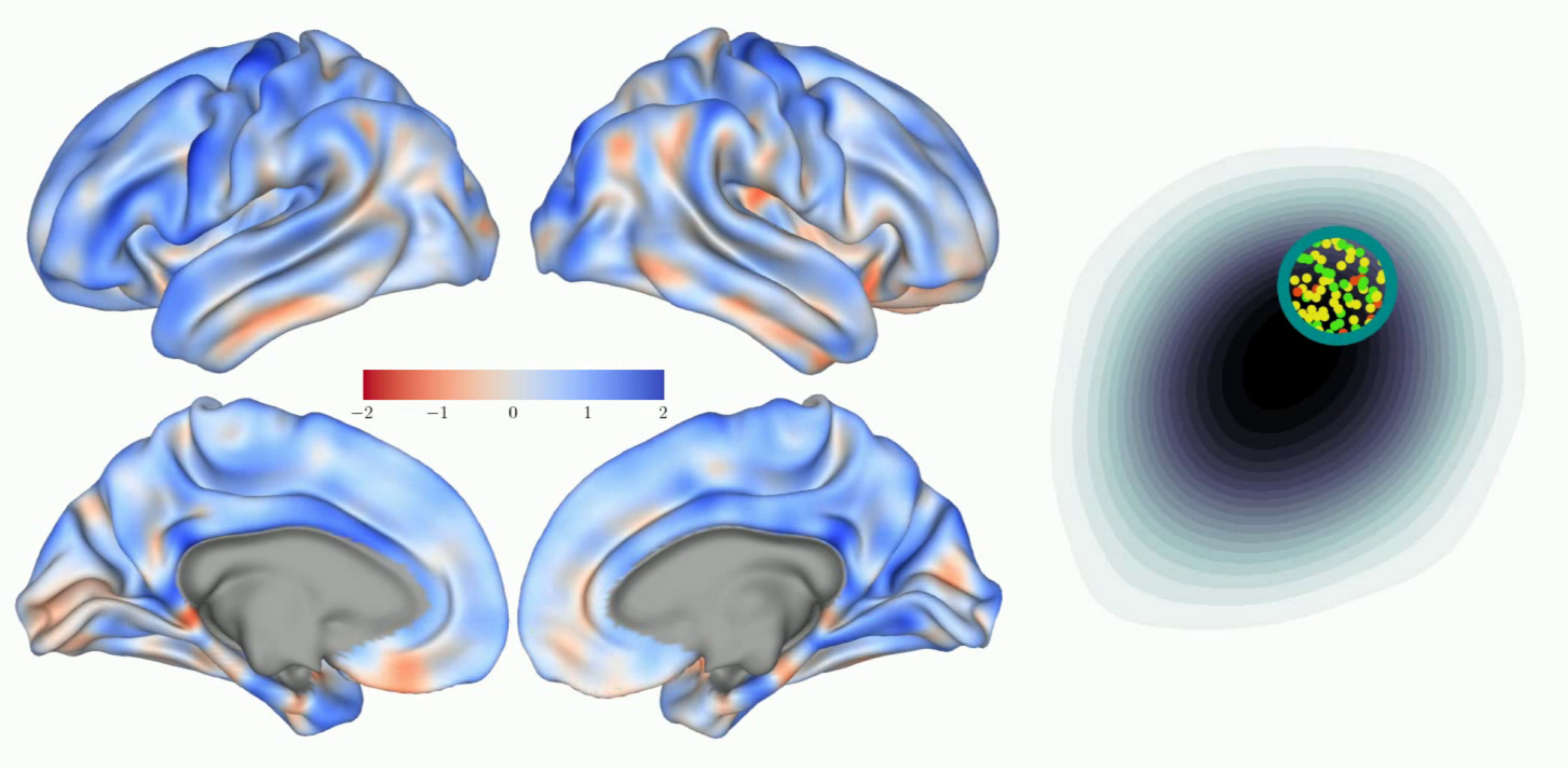

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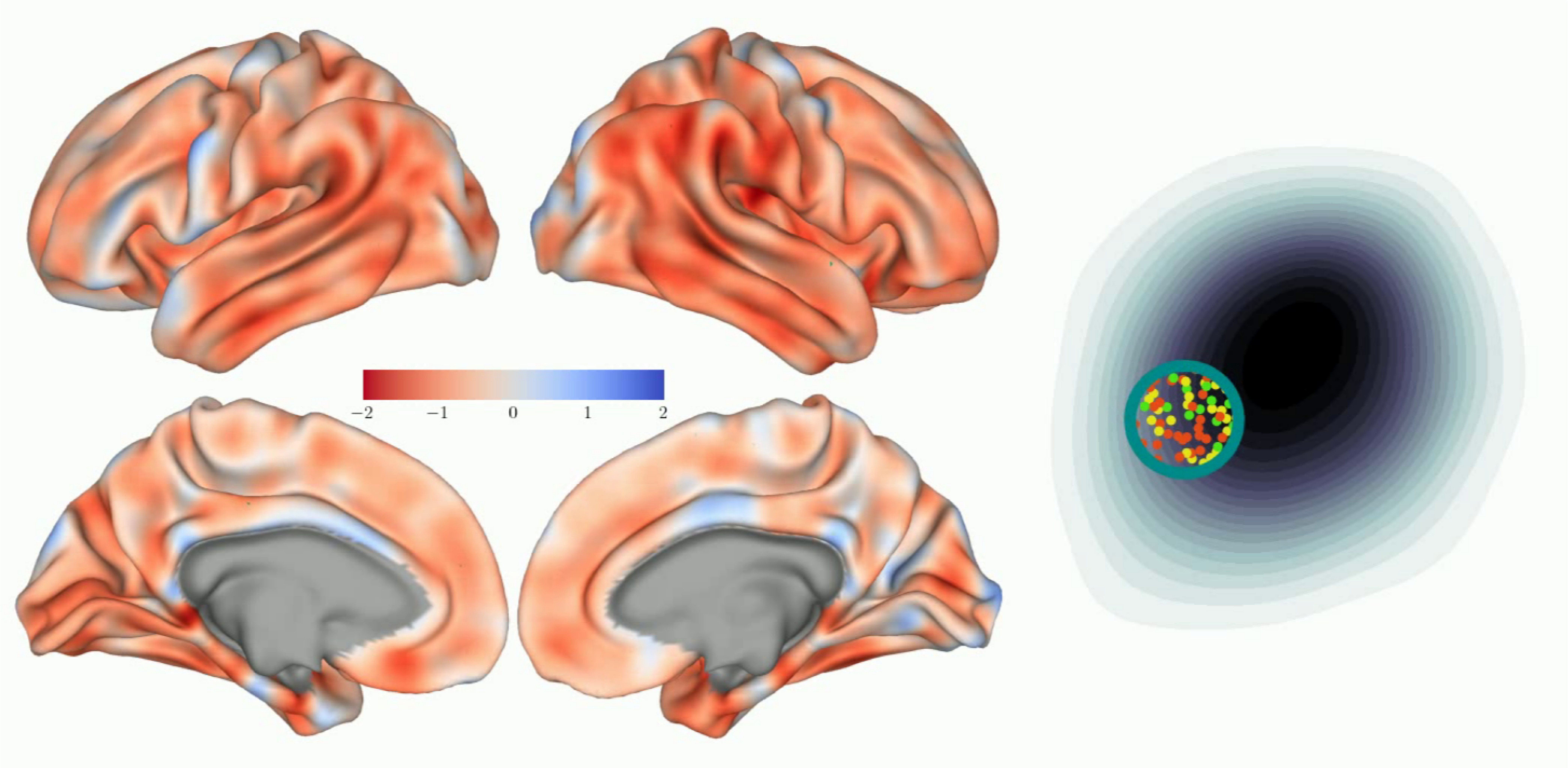

Concluding remarks

Future Directions

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→ GSP & brain eigenmodes provide a powerful basis for compression.

These techniques facilitate processing big data in neuroimaging datasets.

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SNMs unlock new possibilities for personalized medicine in brain imaging.

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Utilizing deeper NN architectures, e.g. using GNNs.

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Presentation slides for the ISMRM Workshop on 40 Years of Diffusion

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