

Charting Multi-Scale Brain Phenotypes Using Spectral Normative Models

Presentation slides for the ISMRM Workshop on 40 Years of Diffusion



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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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Big data in brain imaging

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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

Brain scans are inherently large files

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Example	
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

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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

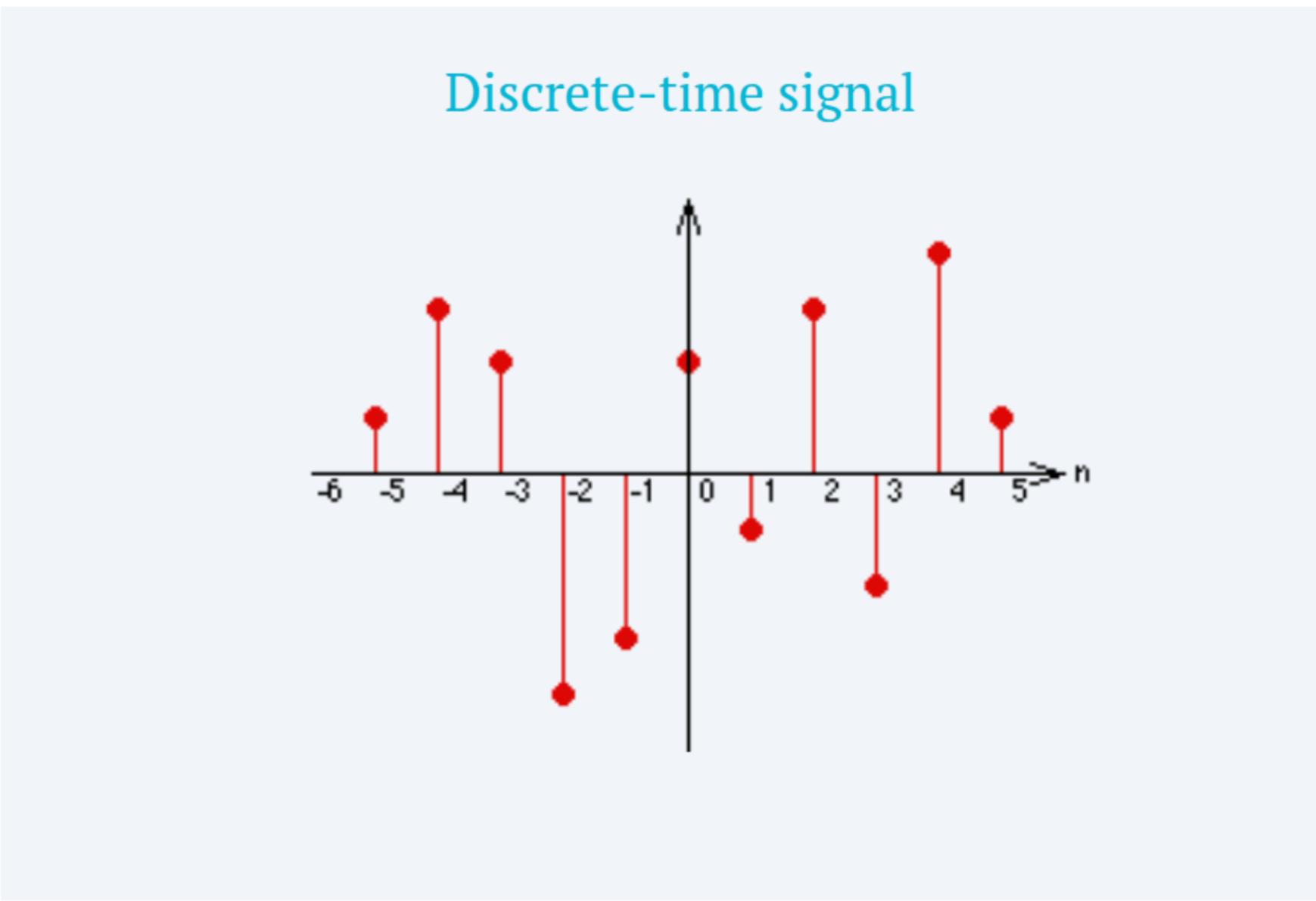
Graph Signal Processing (GSP)

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

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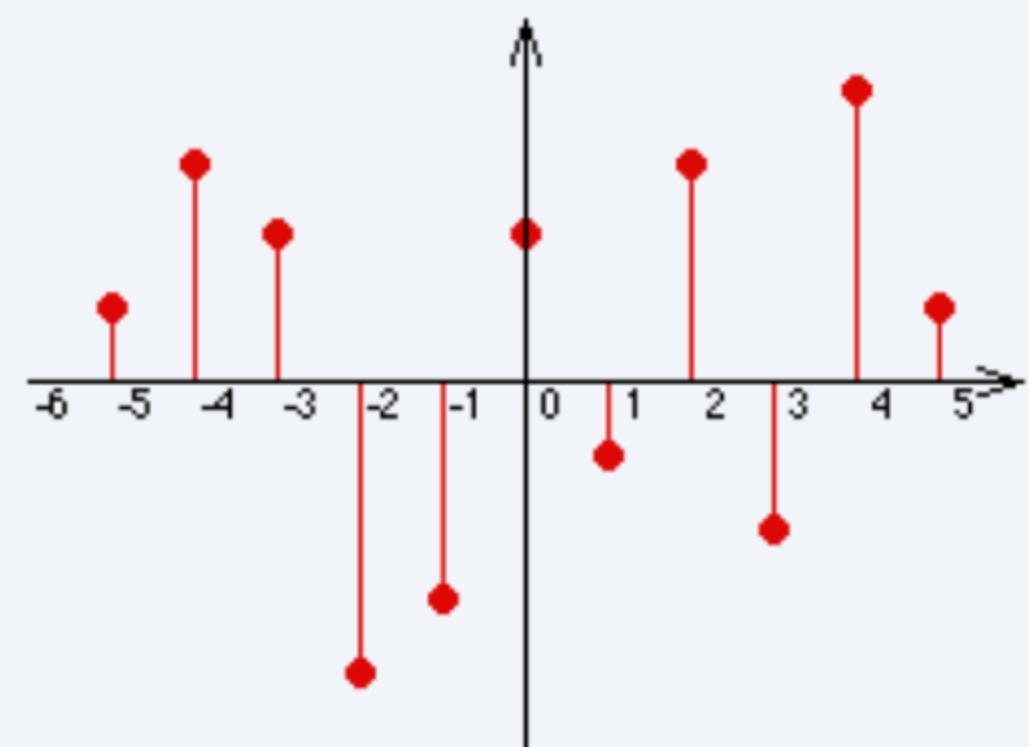
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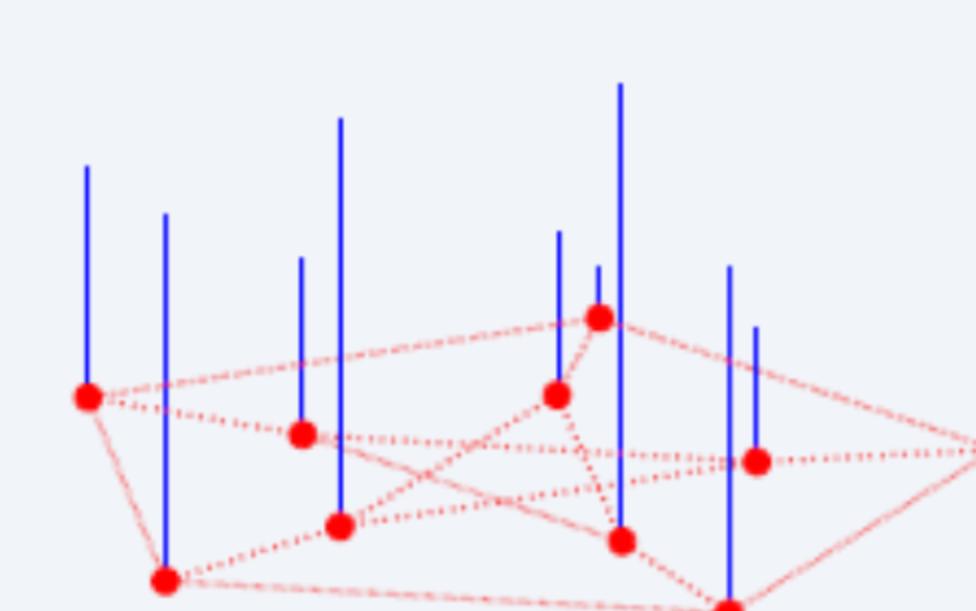
Graph Signal Processing (GSP)

A field of signal processing dedicated to analyzing signals on graphs

Discrete-time signal



Graph Signal: Vector of values over the nodes



Shuman et al. (2013)

Graph Signal Processing (GSP)

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

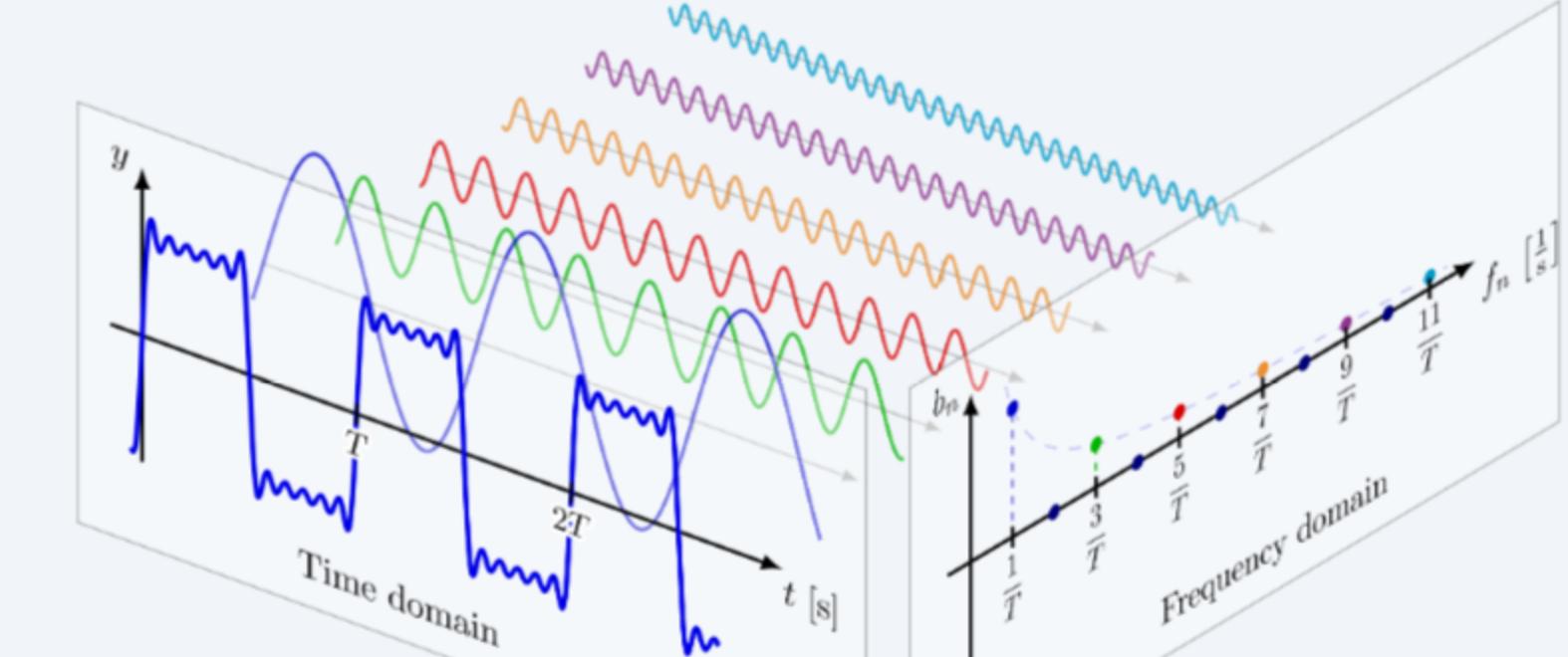
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Discrete Fourier Transform

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



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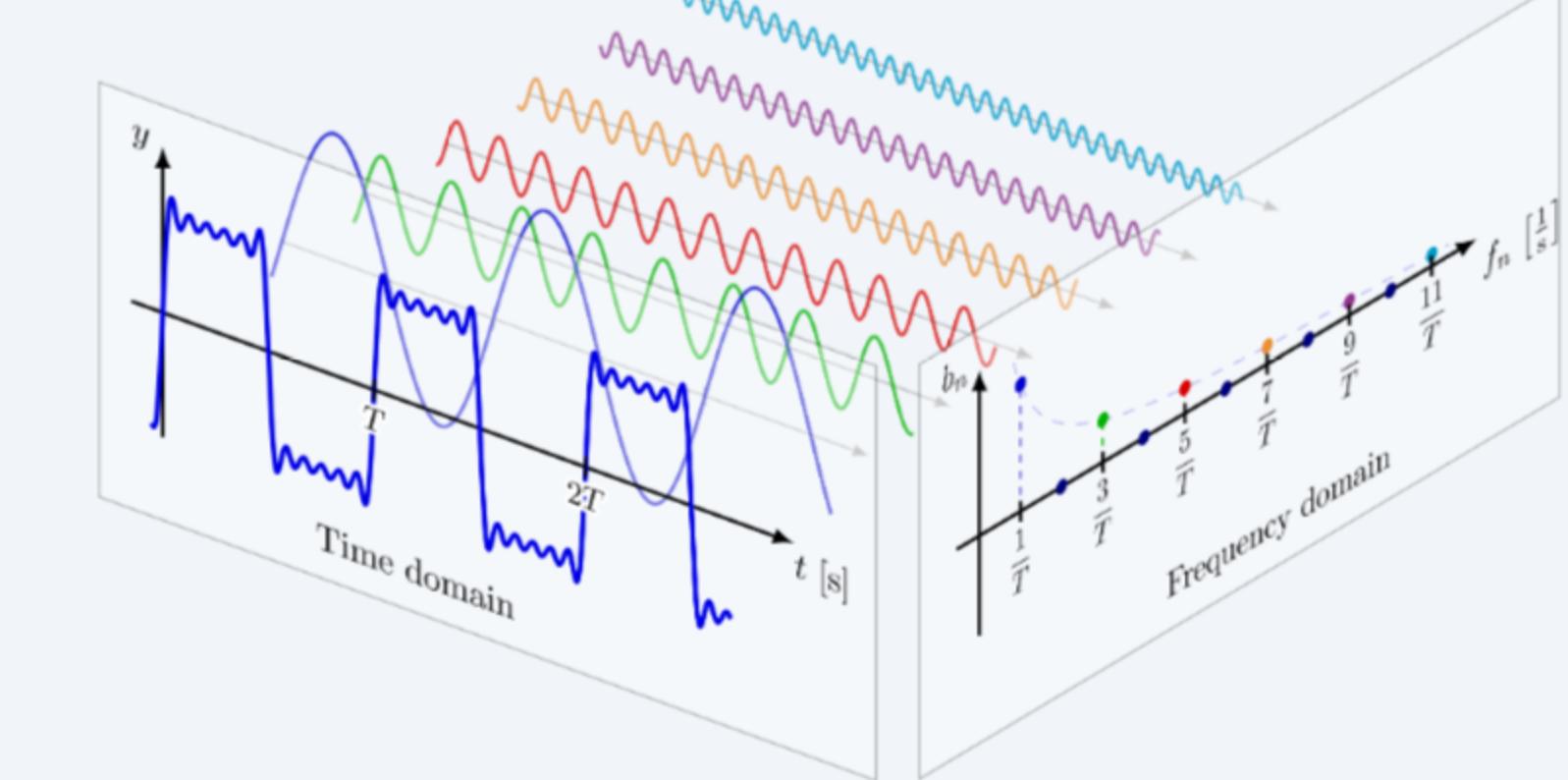
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Time domain



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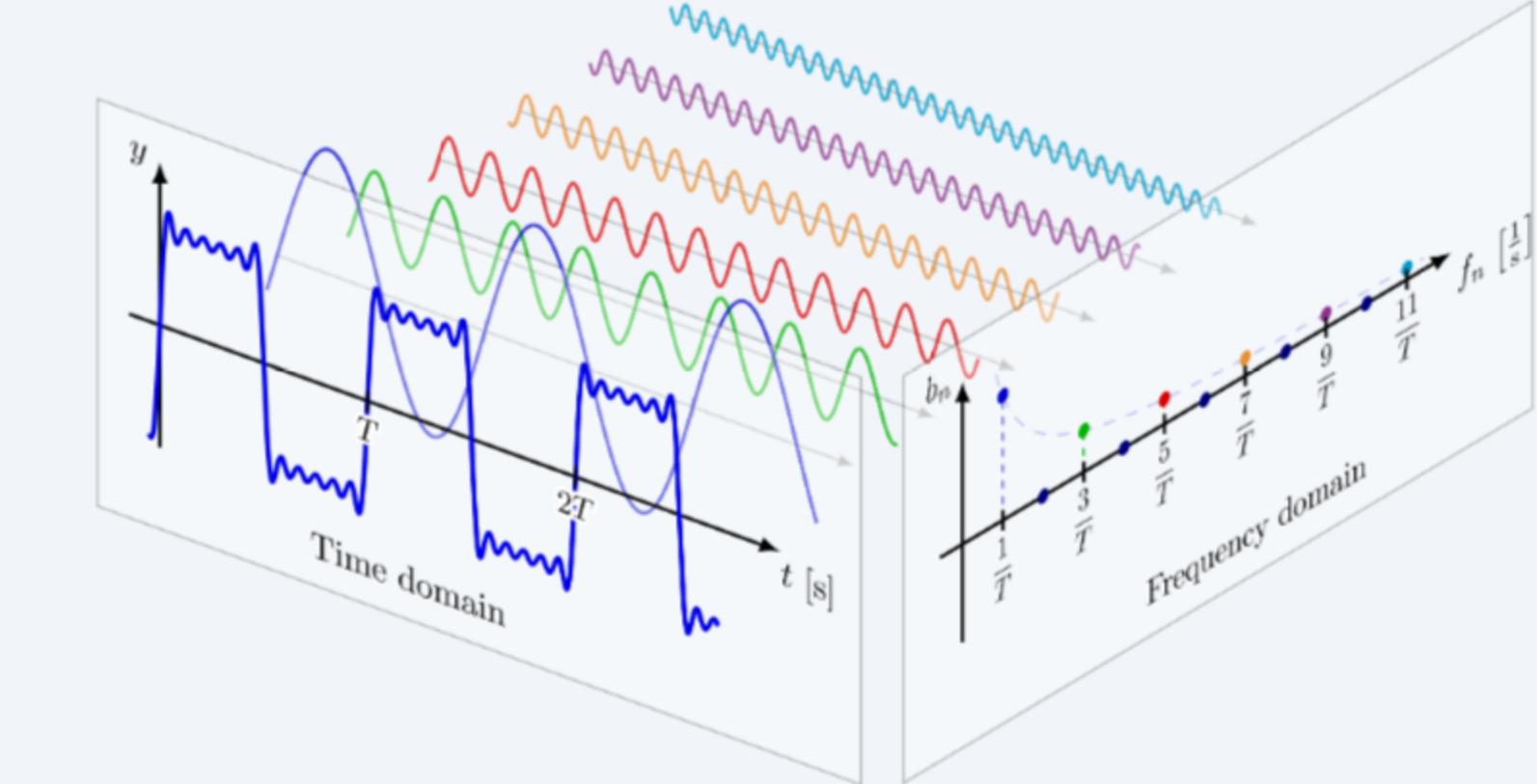
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Frequency domain Time domain



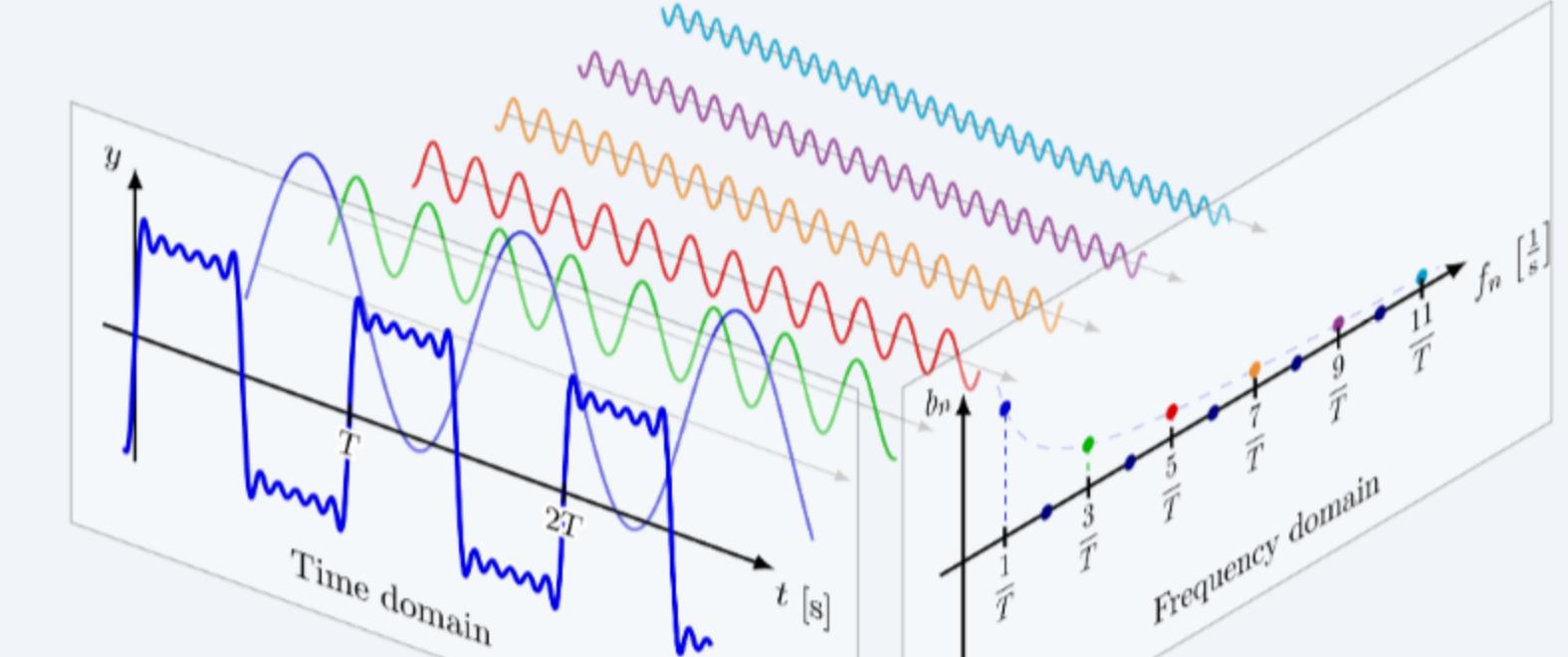
Graph Signal Processing (GSP)

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



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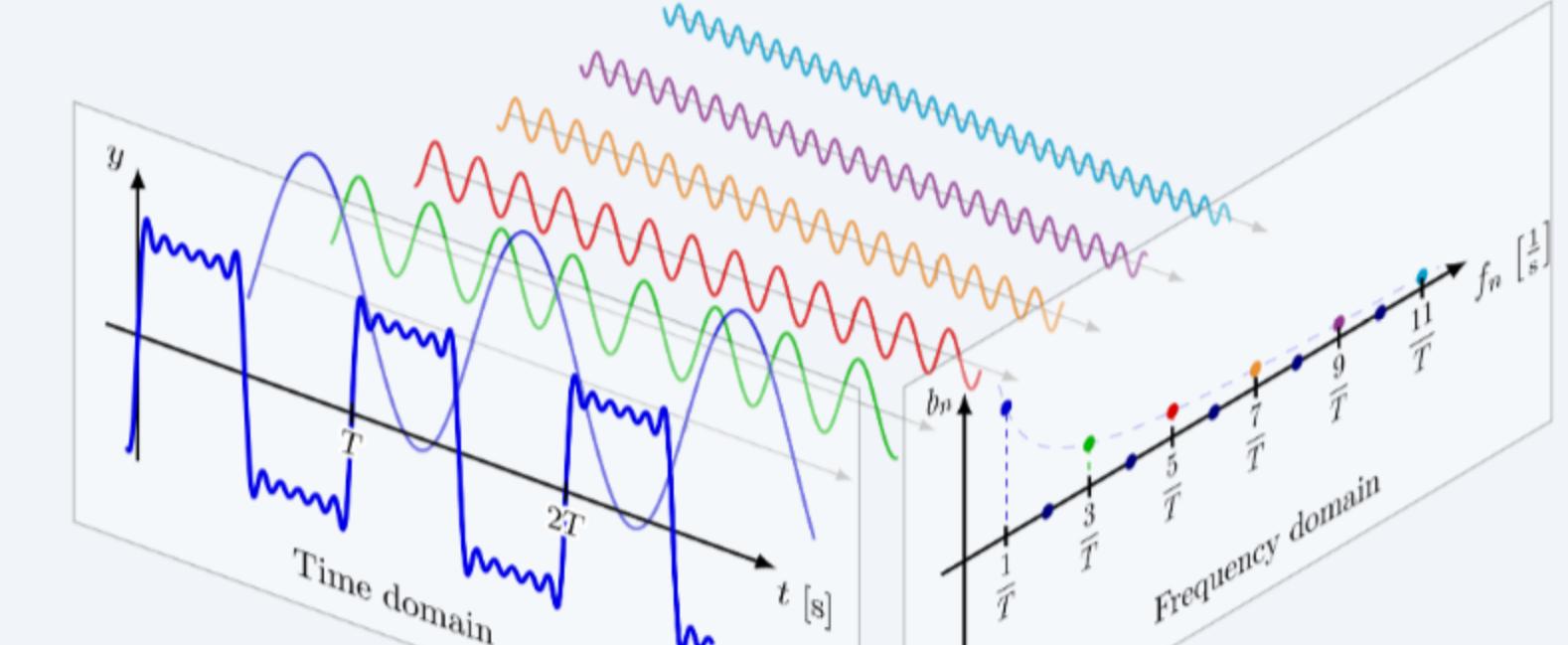
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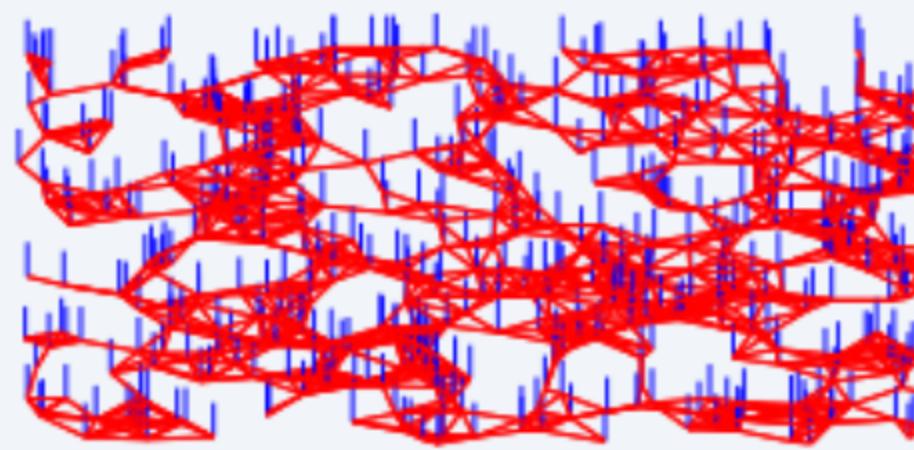
Time domain Frequency domain



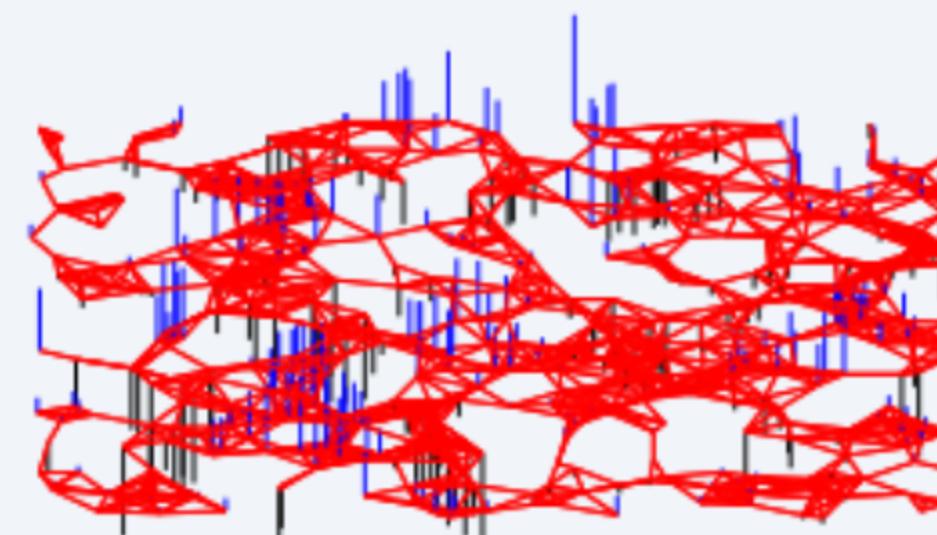
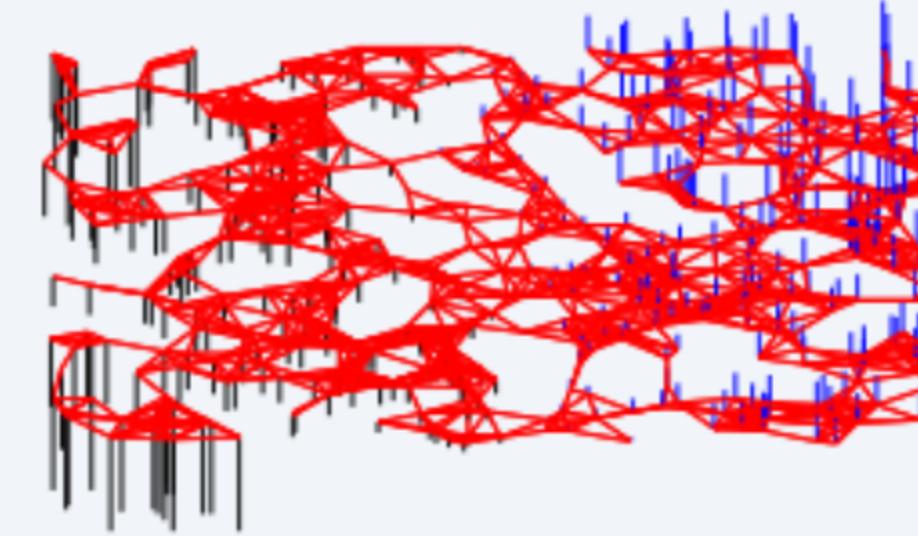
Graph Fourier Transform (GFT)

Graph Fourier Transform (GFT)

→ 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

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

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Analogous to DFT, but for graphs

GFT is defined using a graph shift operator

→ Graph Fourier basis via singular value decomposition of shift operator

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

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

Huang et al. (2018)

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Graph
signal
domain

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

Huang et al. (2018)

The diagram shows the Graph Fourier Transform equation $\tilde{\mathbf{X}} = \mathbf{V}^\top \mathbf{X}$. The term $\tilde{\mathbf{X}}$ is highlighted with a red oval and labeled "Graph frequency domain". The term \mathbf{X} is also highlighted with a red oval and labeled "Graph signal domain". The equation is centered above the citation "Huang et al. (2018)".

Graph Fourier Transform (GFT)

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$$\mathbf{X} = \mathbf{V}\widetilde{\mathbf{X}}$$

Huang et al. (2018)

The diagram illustrates the inverse Graph Fourier Transform equation. It features a central equality sign between two terms. To the left of the first term, \mathbf{X} , is the text "Graph signal domain" in red. To the right of the second term, $\mathbf{V}\widetilde{\mathbf{X}}$, is the text "Graph frequency domain" in red. Both terms are enclosed within red ovals.

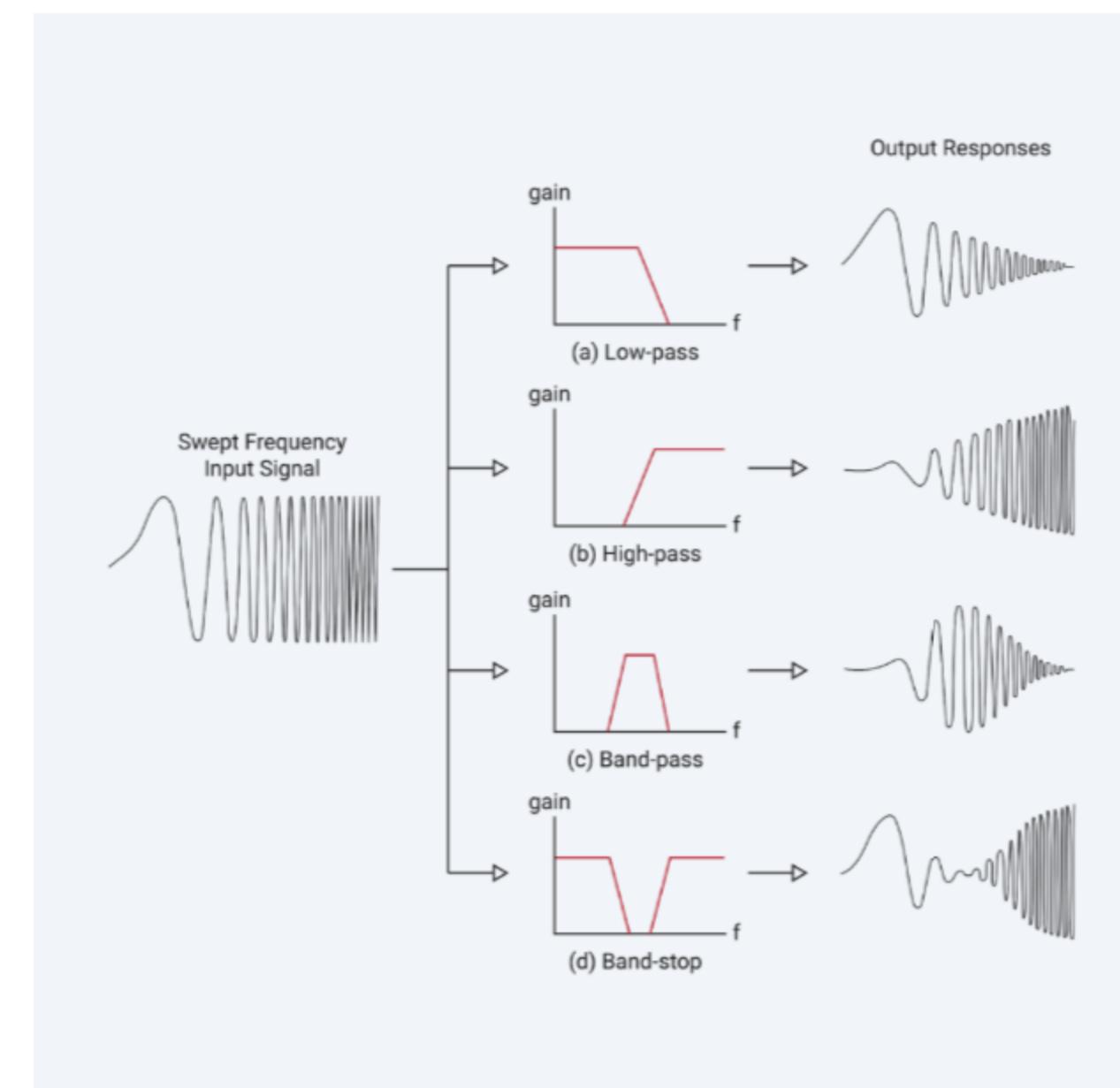
Graph Filters

Graph Filters

→ Idea: Reconstruct particular frequency bands of the signal

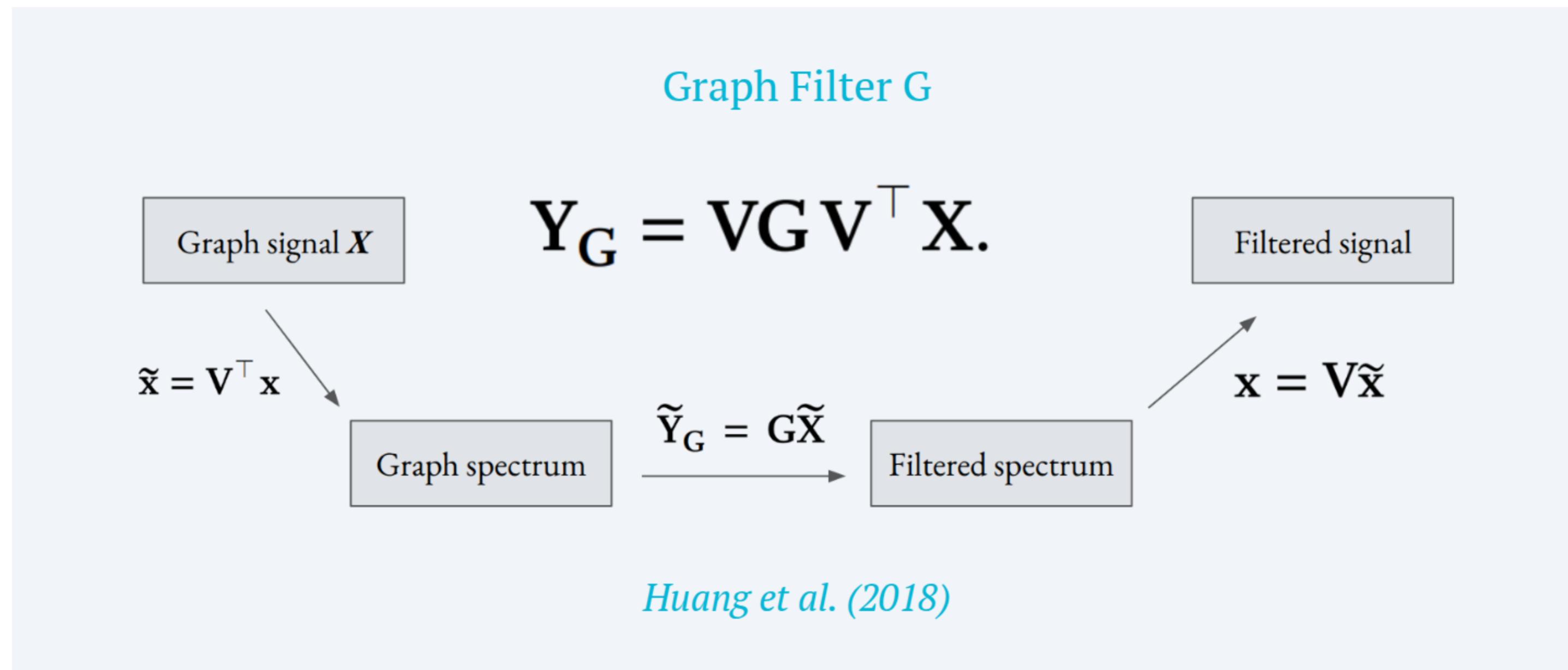
Graph Filters

Idea: Reconstruct particular frequency bands of the signal



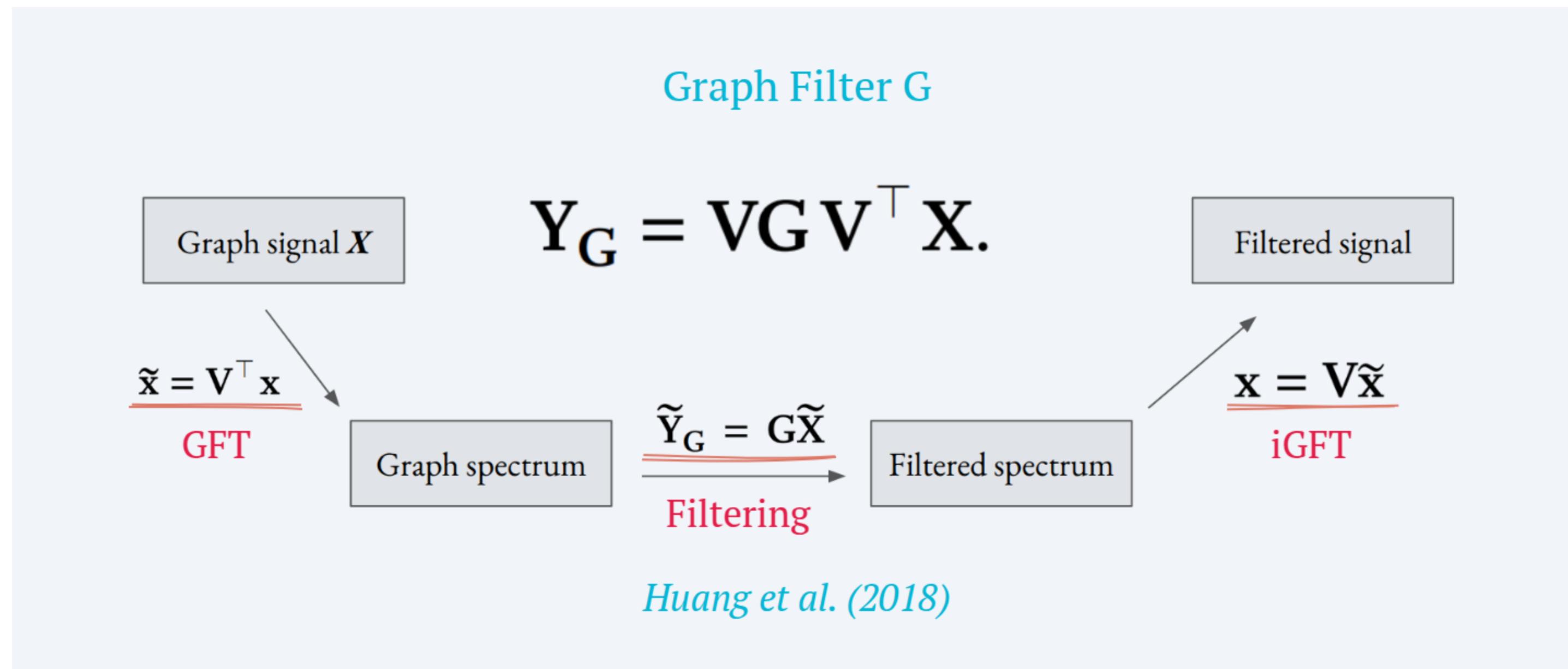
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Idea: Reconstruct particular frequency bands of the signal



Graph Filters

Idea: Reconstruct particular frequency bands of the signal



Network Neuroscience and GSP on brain graphs

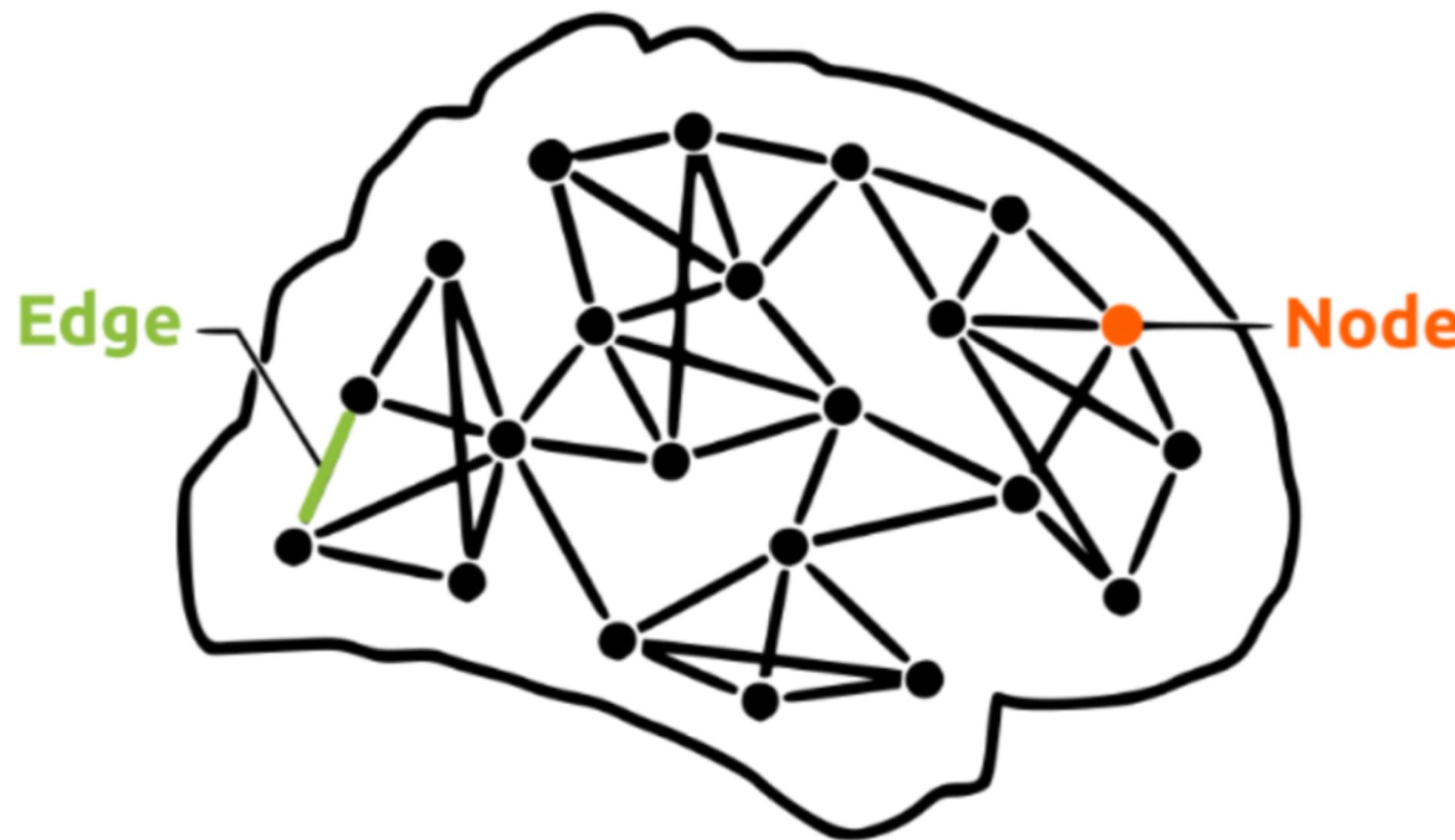
Network Neuroscience and GSP on brain graphs

→ Modeling anatomical brain networks



Network Neuroscience and GSP on brain graphs

Modeling anatomical brain networks



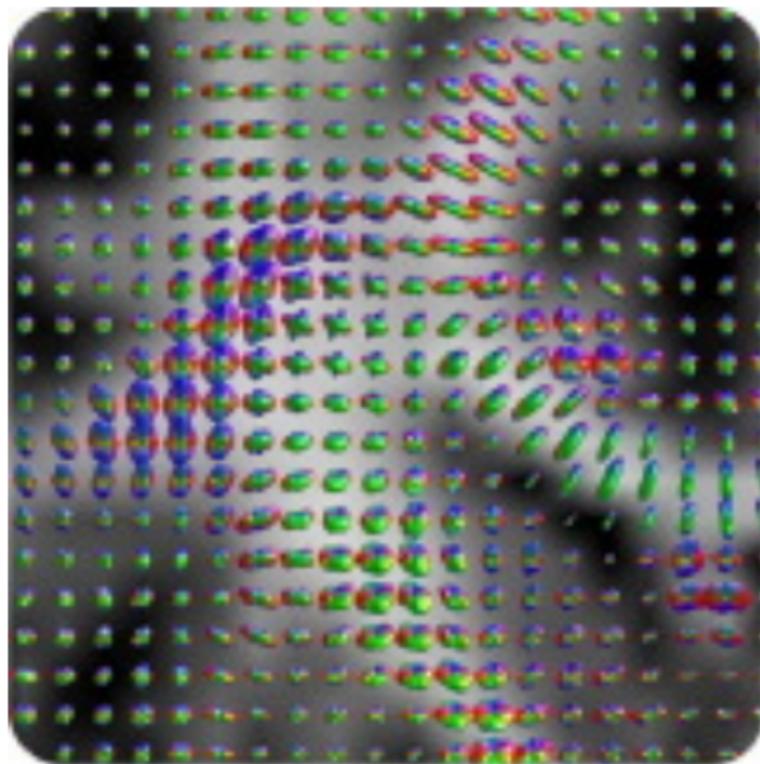
Diffusion MRI data

Diffusion MRI data

- Enables mapping in-vivo anatomical wiring networks

Diffusion MRI data

Enables mapping in-vivo anatomical wiring networks

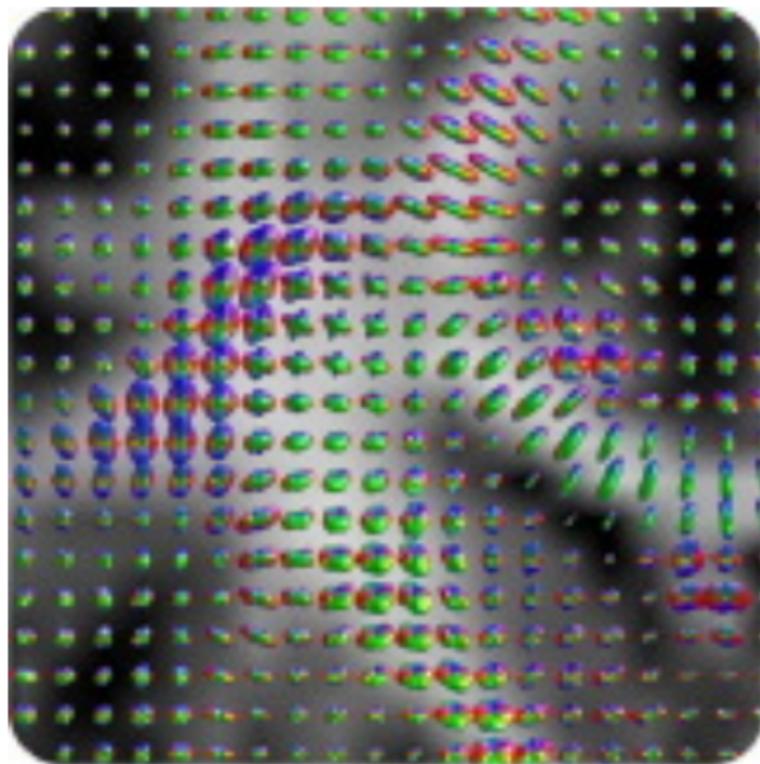


raw dMRI signal

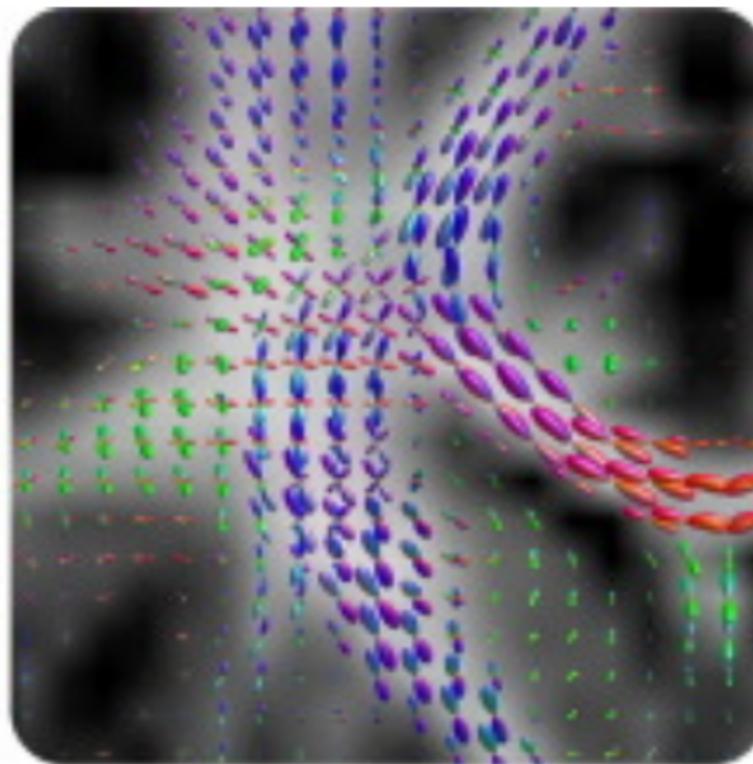
Tournier 2019

Diffusion MRI data

Enables mapping in-vivo anatomical wiring networks



raw dMRI signal

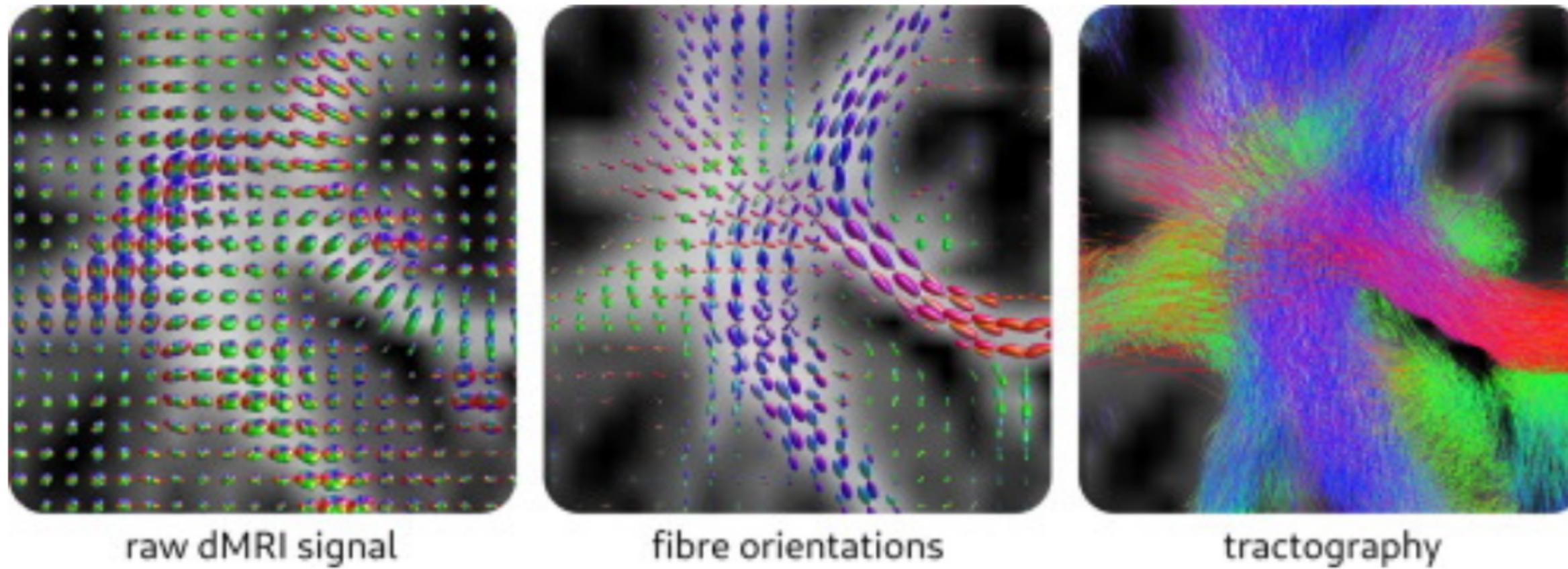


fibre orientations

Tournier 2019

Diffusion MRI data

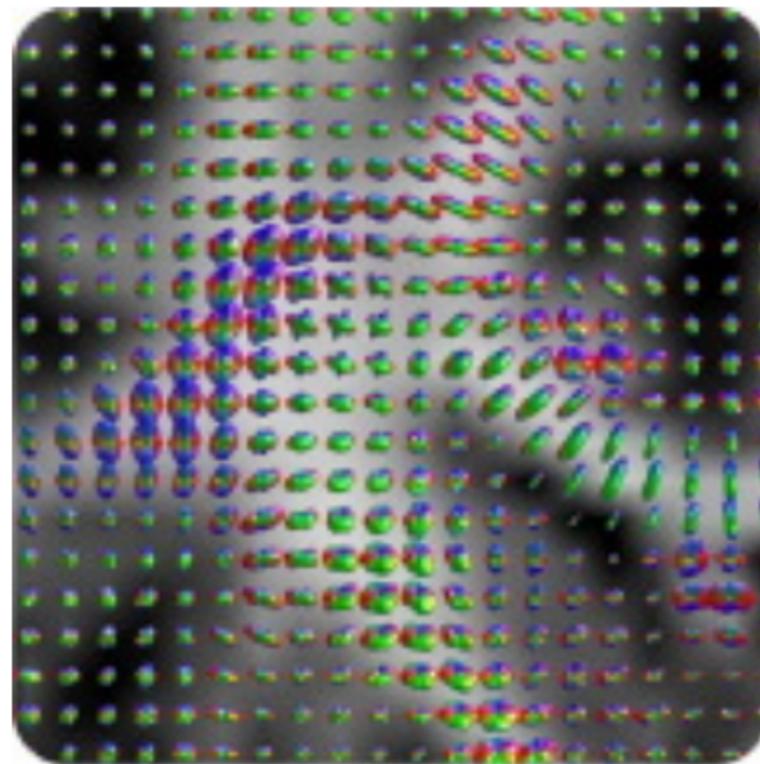
Enables mapping in-vivo anatomical wiring networks



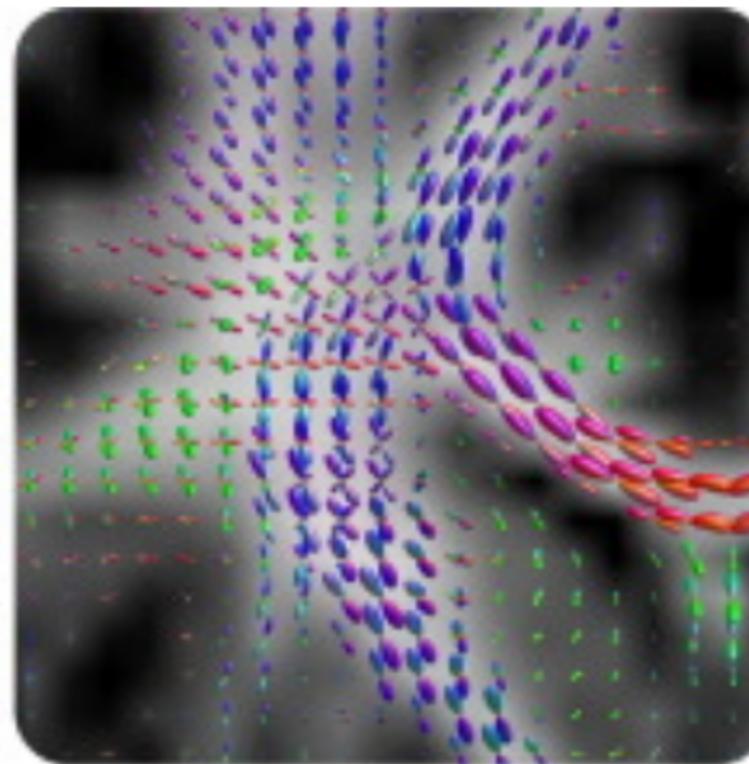
Tournier 2019

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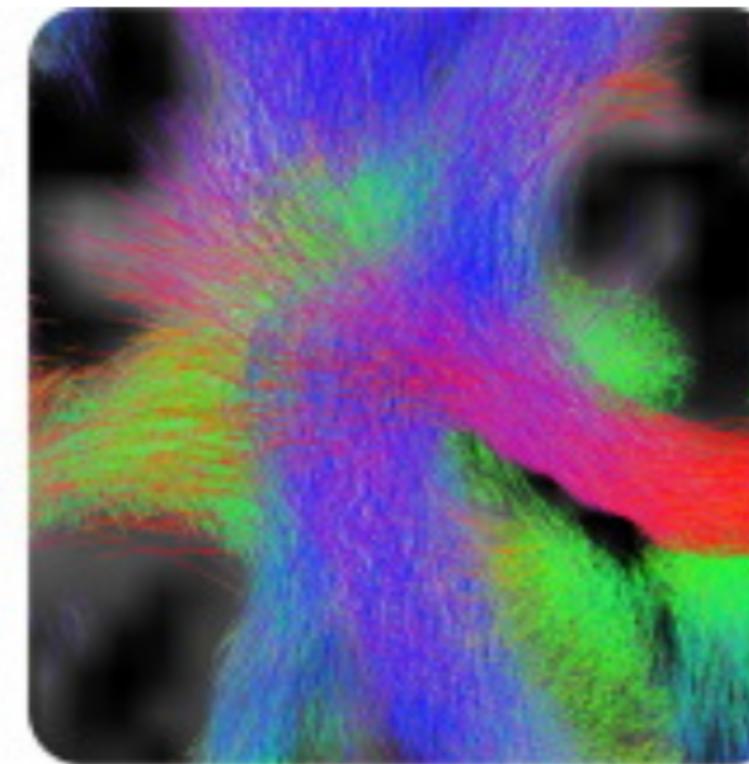
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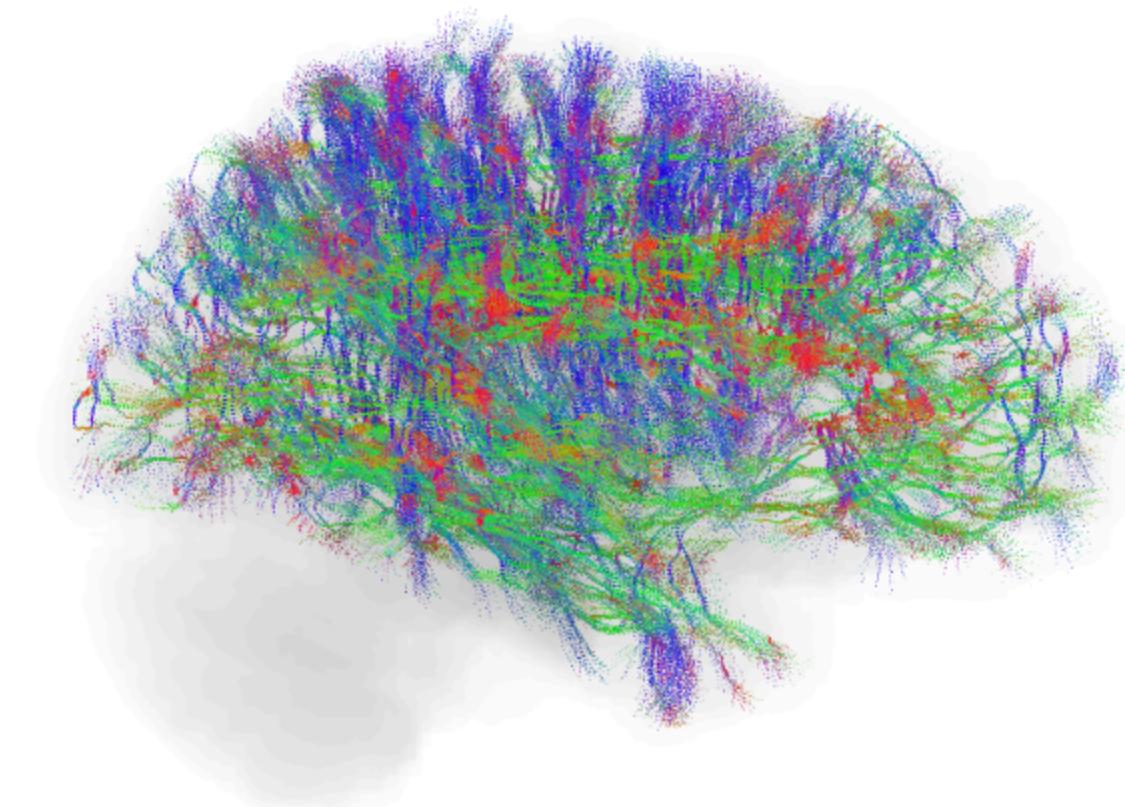
raw dMRI signal



fibre orientations



tractography

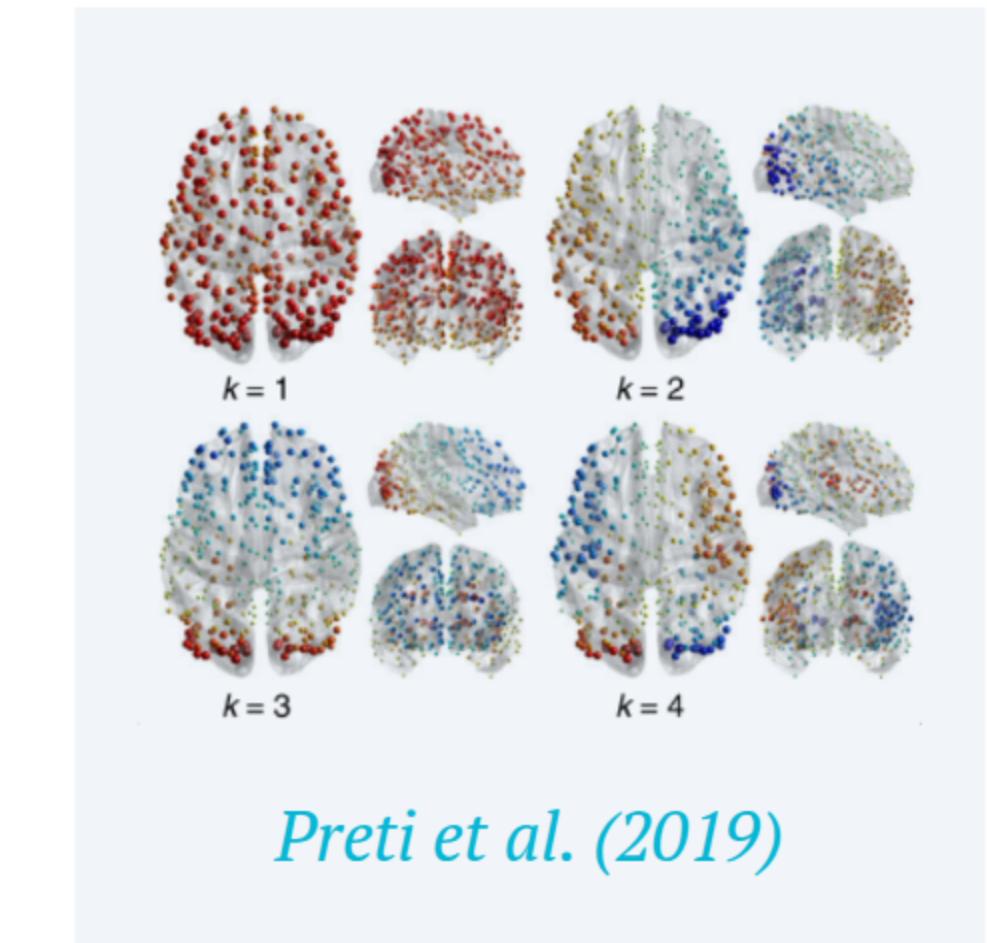
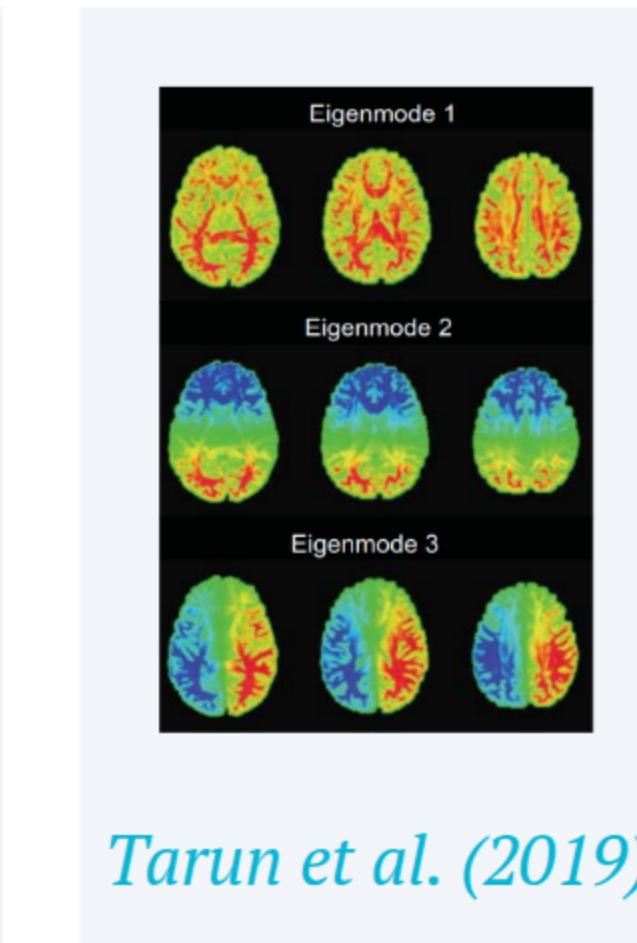
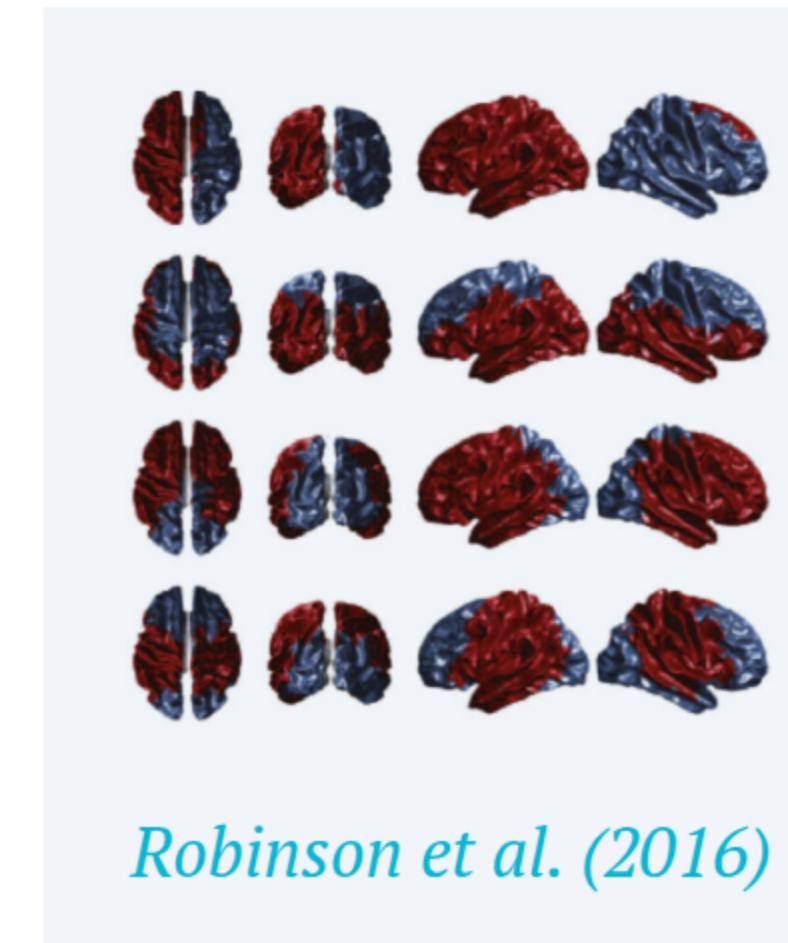
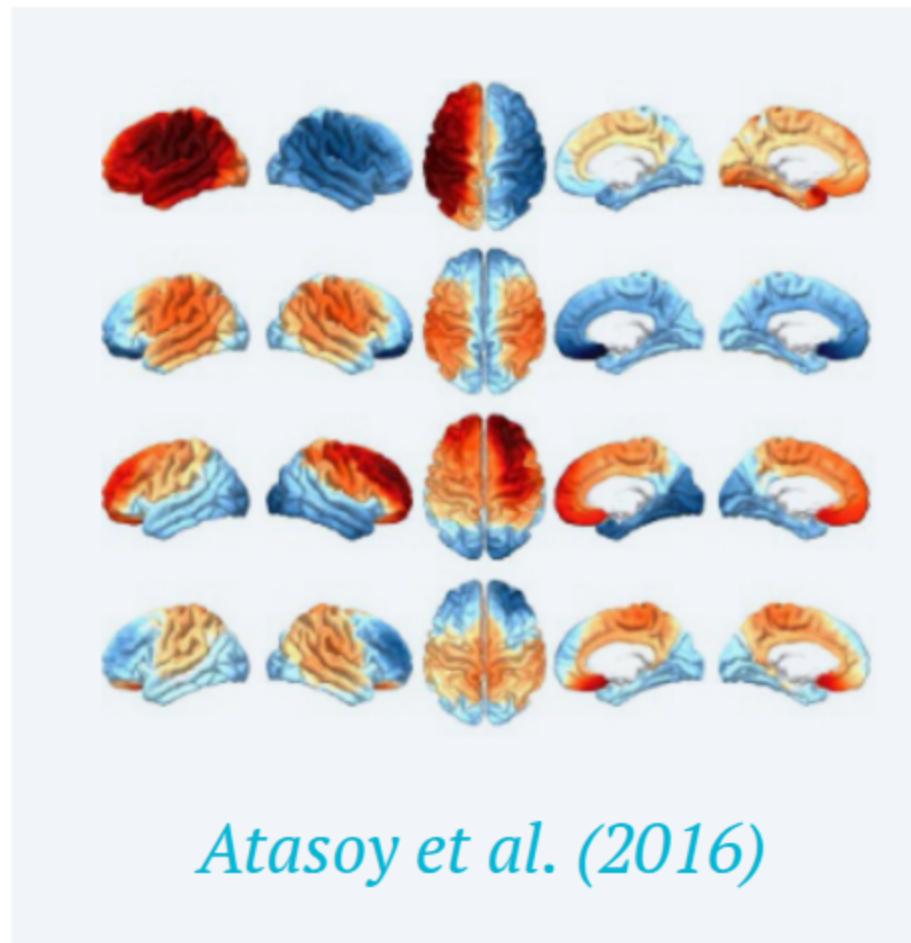


Tournier 2019

GSP in brain imaging

GSP in brain imaging

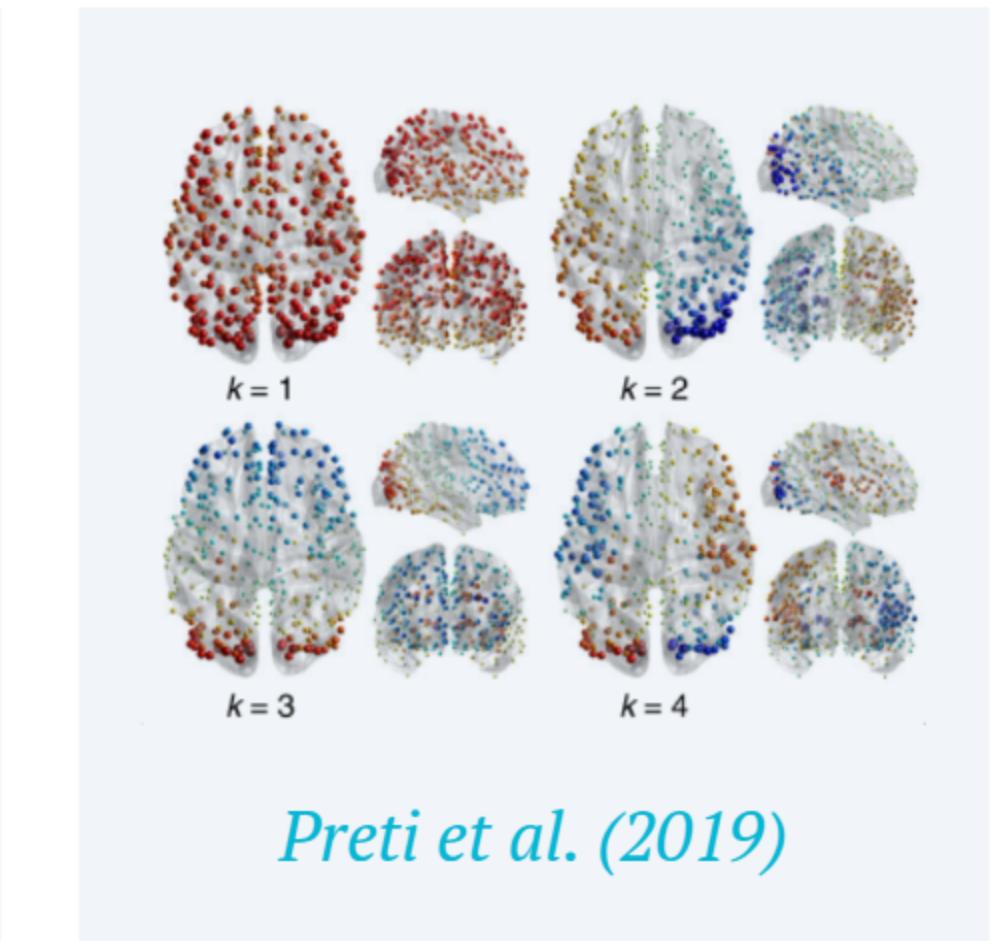
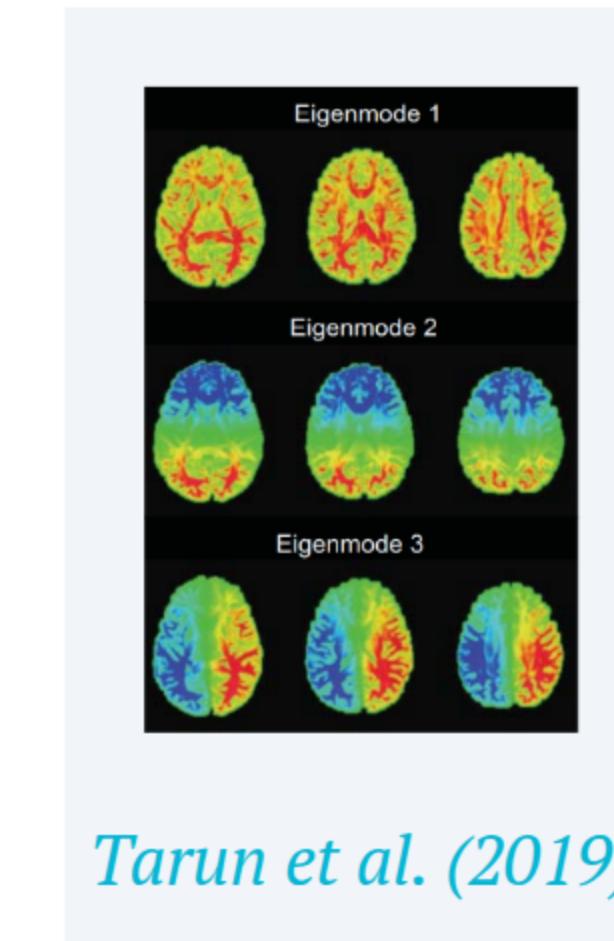
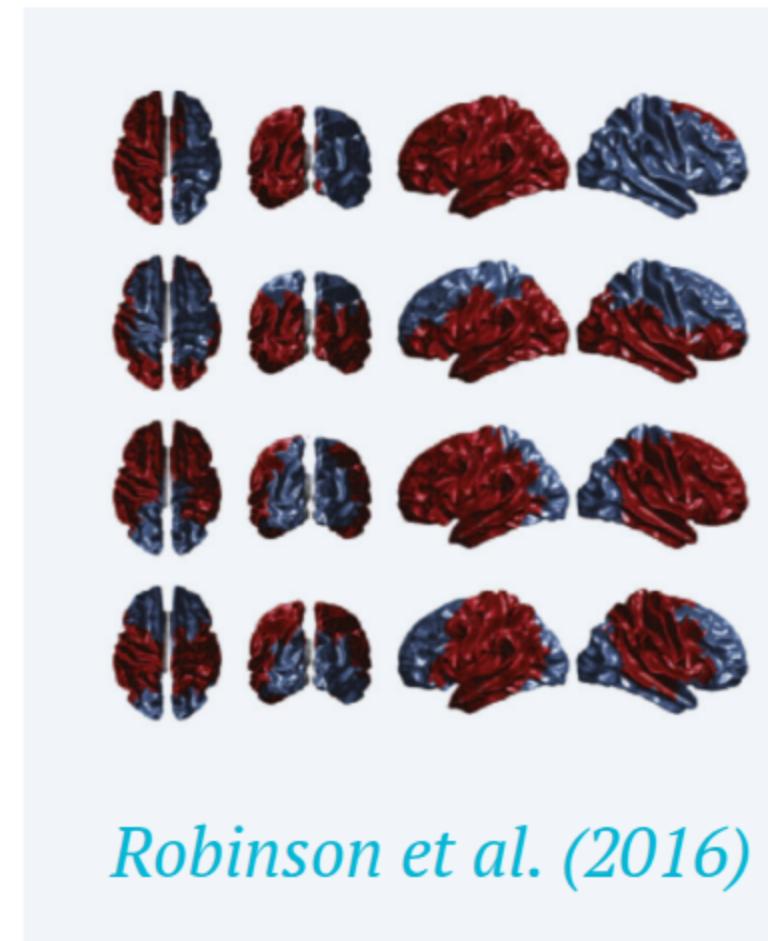
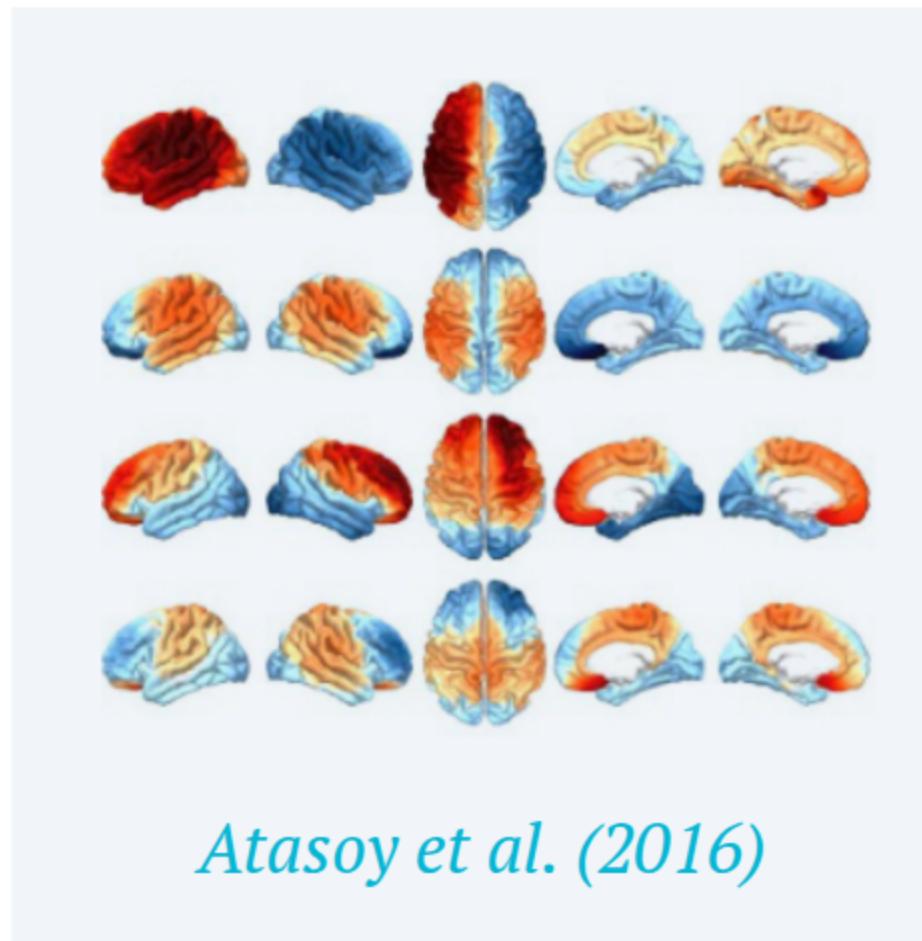
→ GSP methods have been used to study brain signals in the past decade



GSP in brain imaging

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

→ Different terminologies: harmonics, eigenmodes, gradients, ...



High-resolution connectome eigenmodes

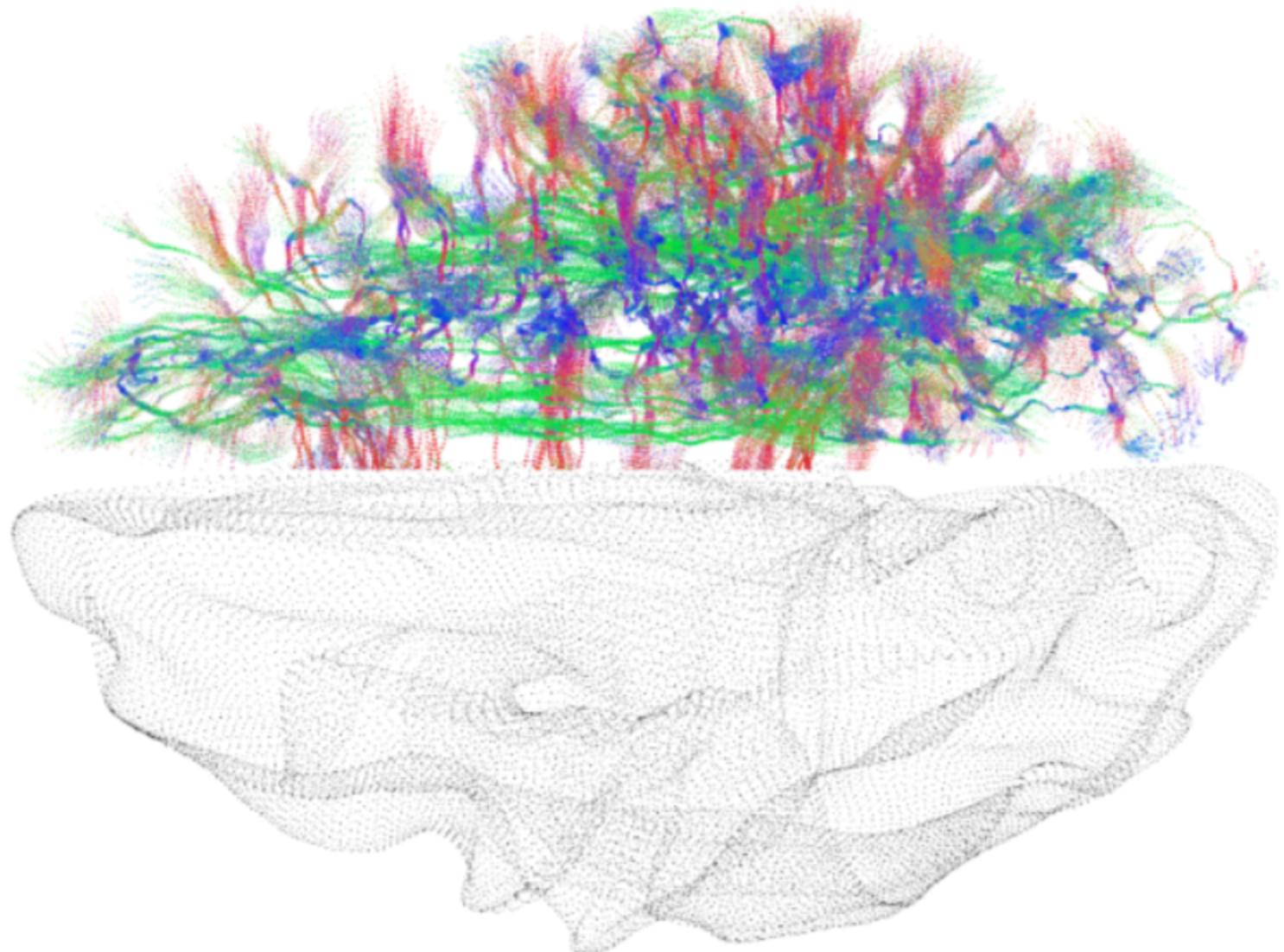
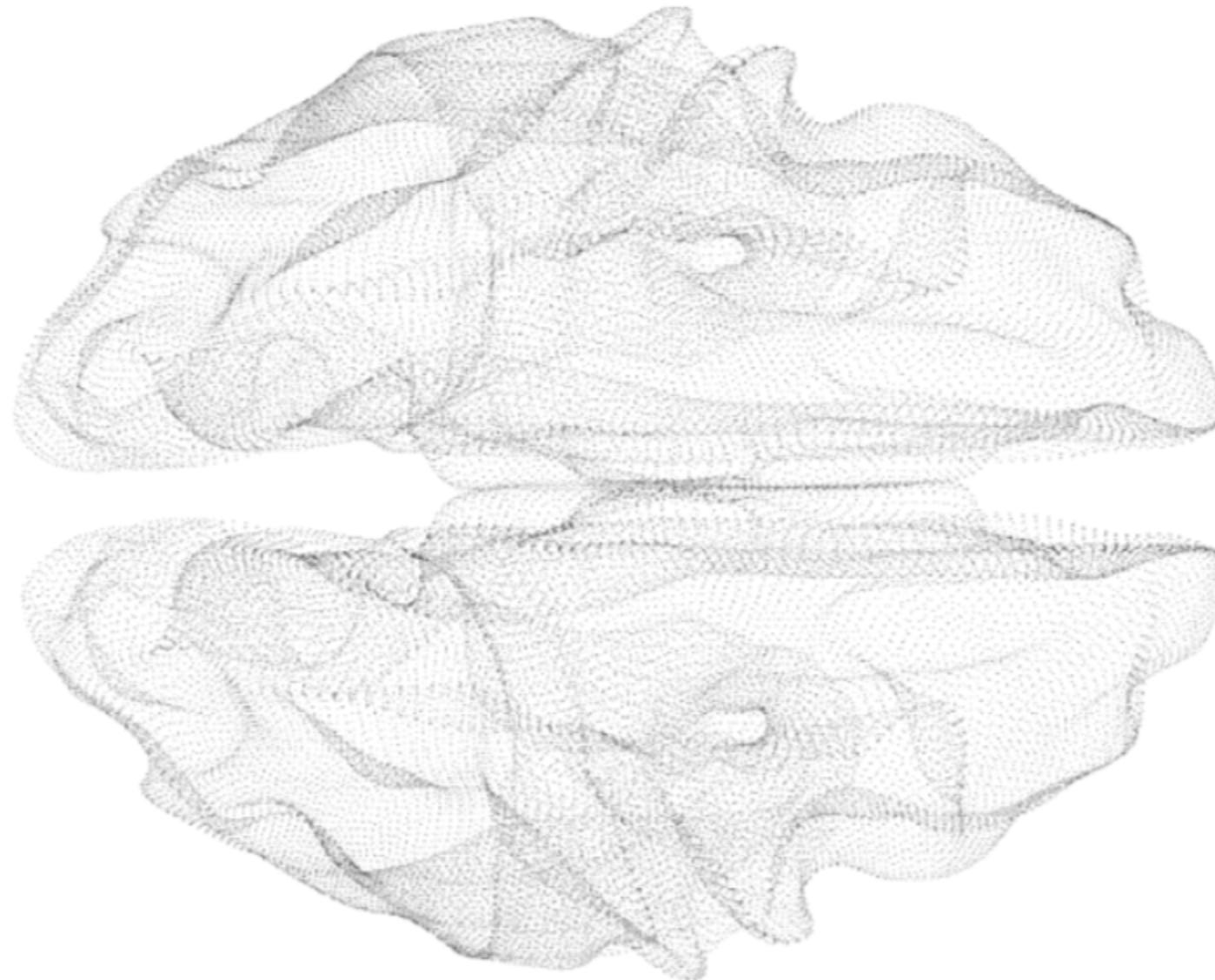
High-resolution connectome eigenmodes

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

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)

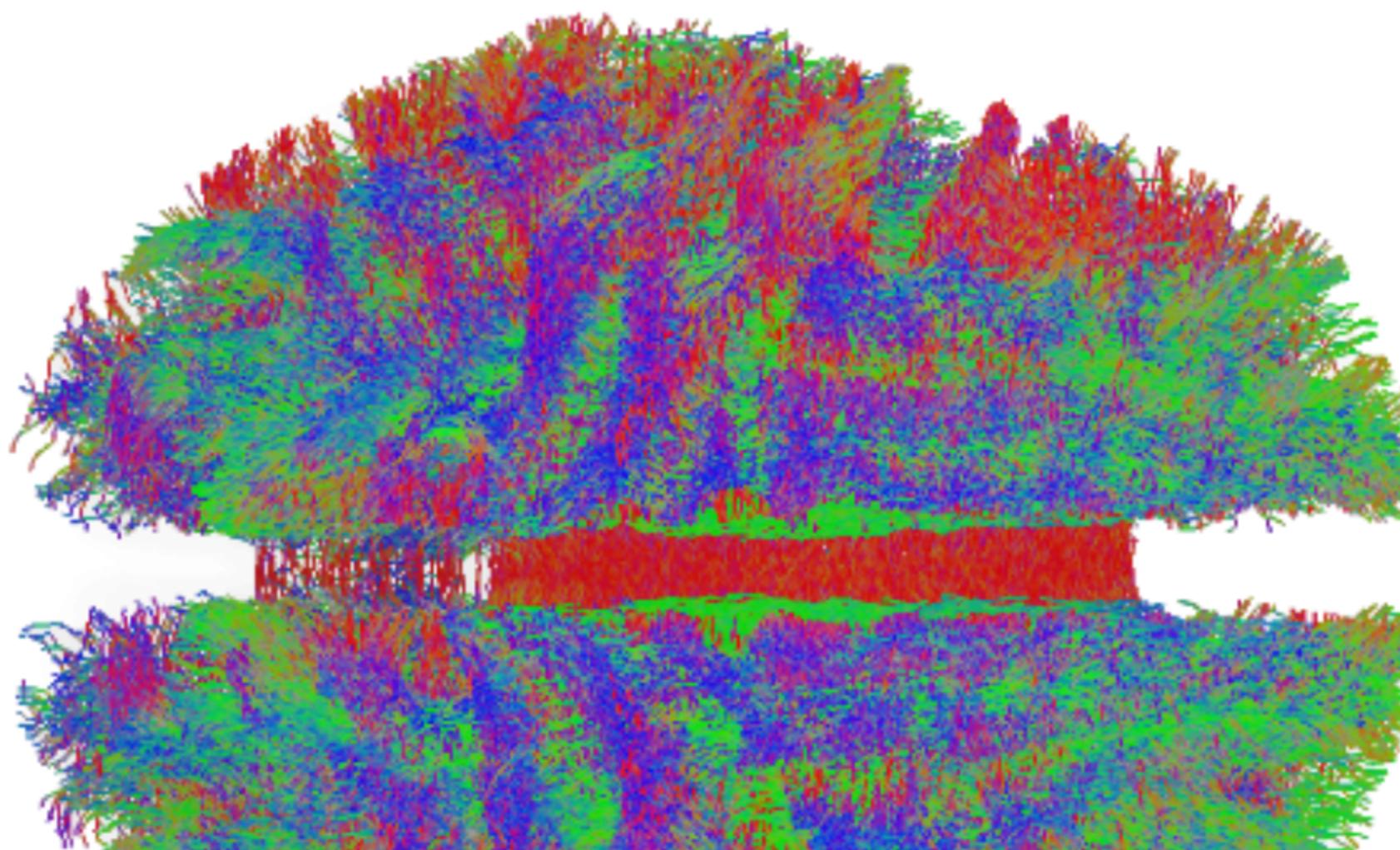


High-resolution connectome eigenmodes

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



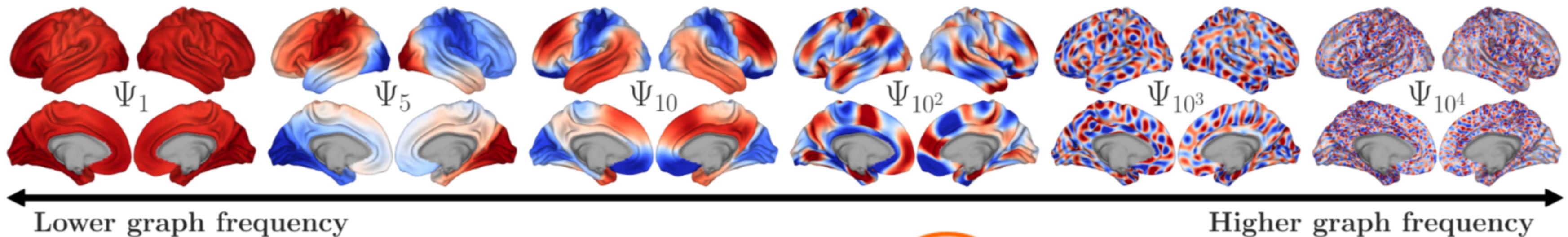
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Perform tractography over a large sample (e.g. HCP YA)

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



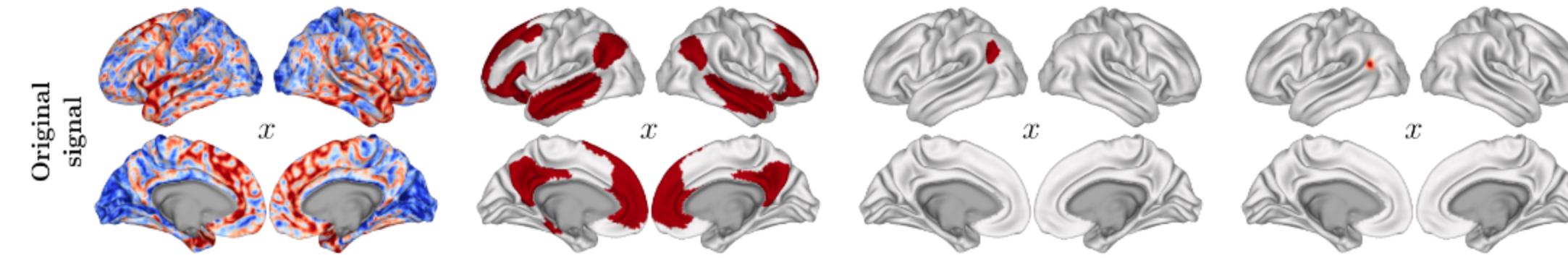
$$\text{Signal } \leftarrow X = \sum_i \alpha_i \psi_i + \varepsilon = \hat{X} + \varepsilon \quad \xrightarrow{\text{Reconstruction}}$$

Signal reconstruction via eigenmodes:

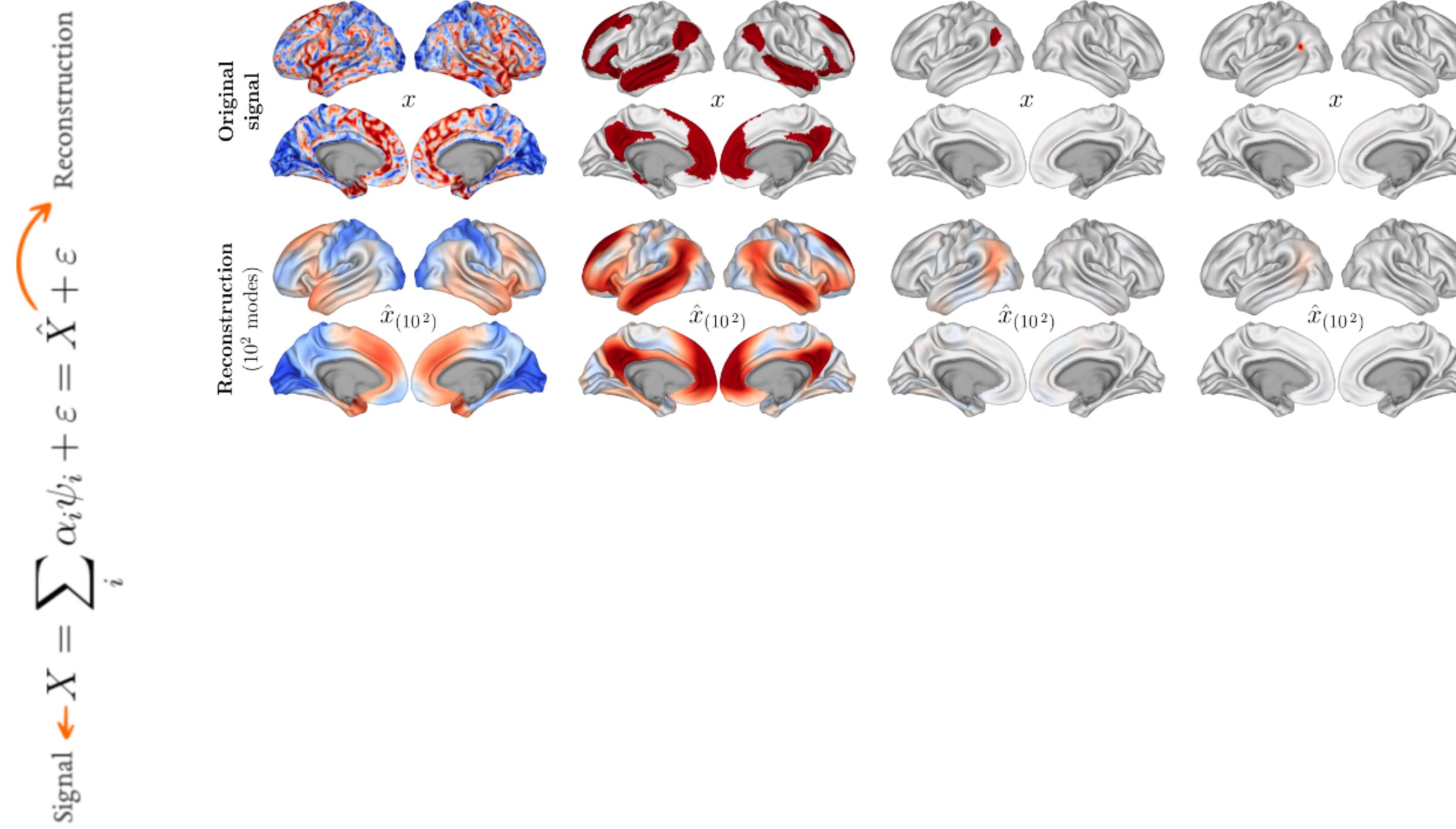
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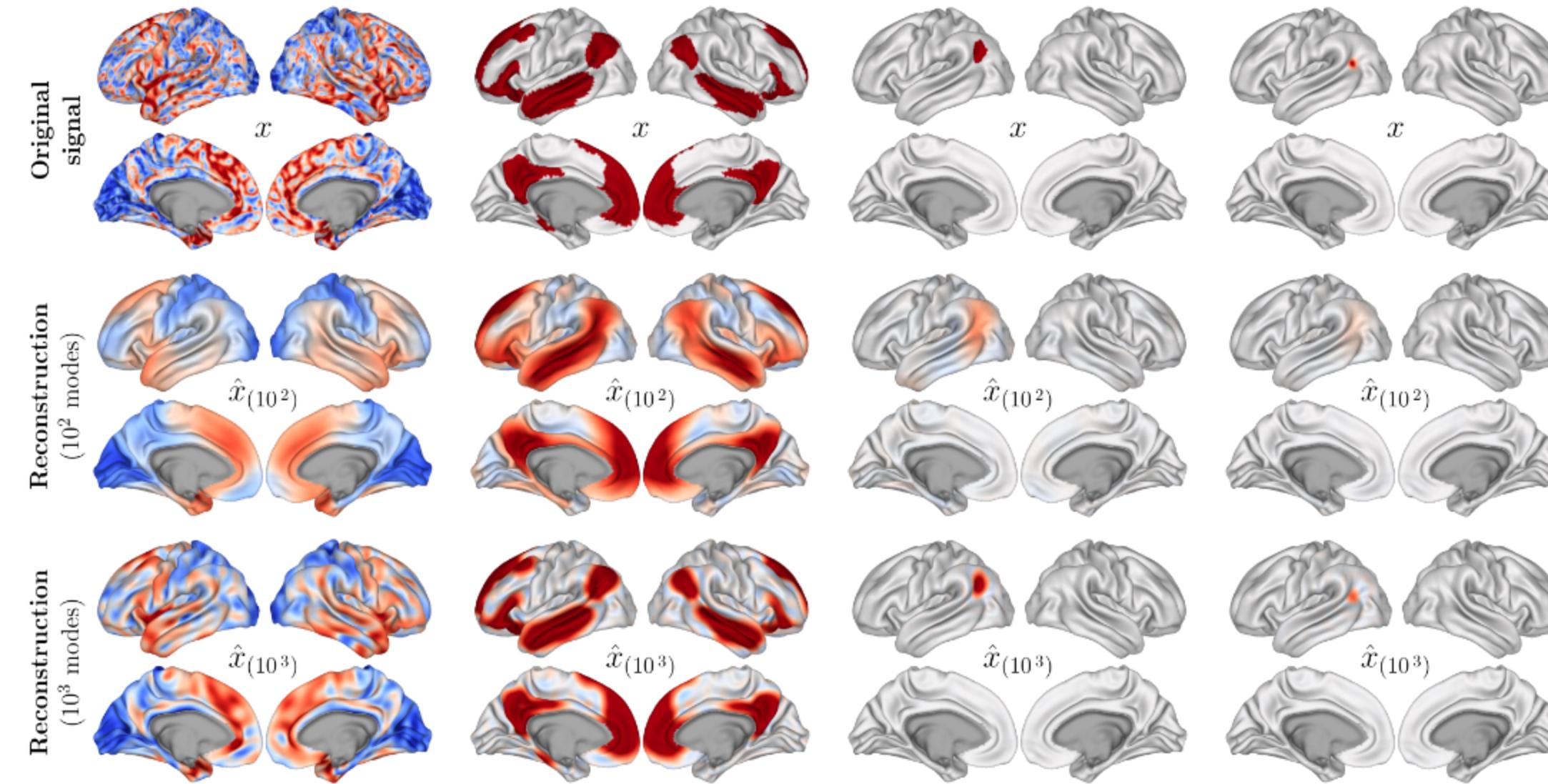


Signal reconstruction via eigenmodes:



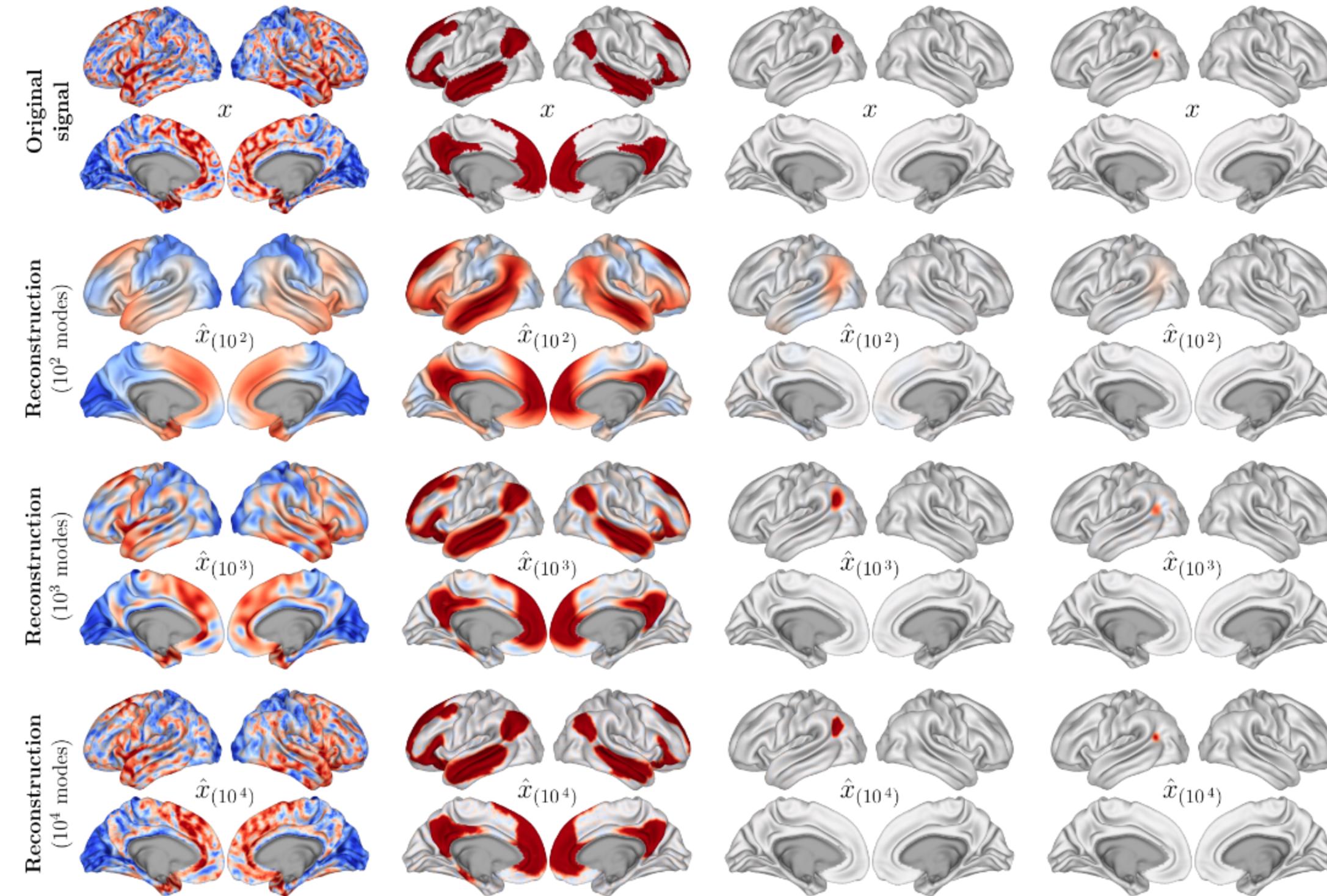
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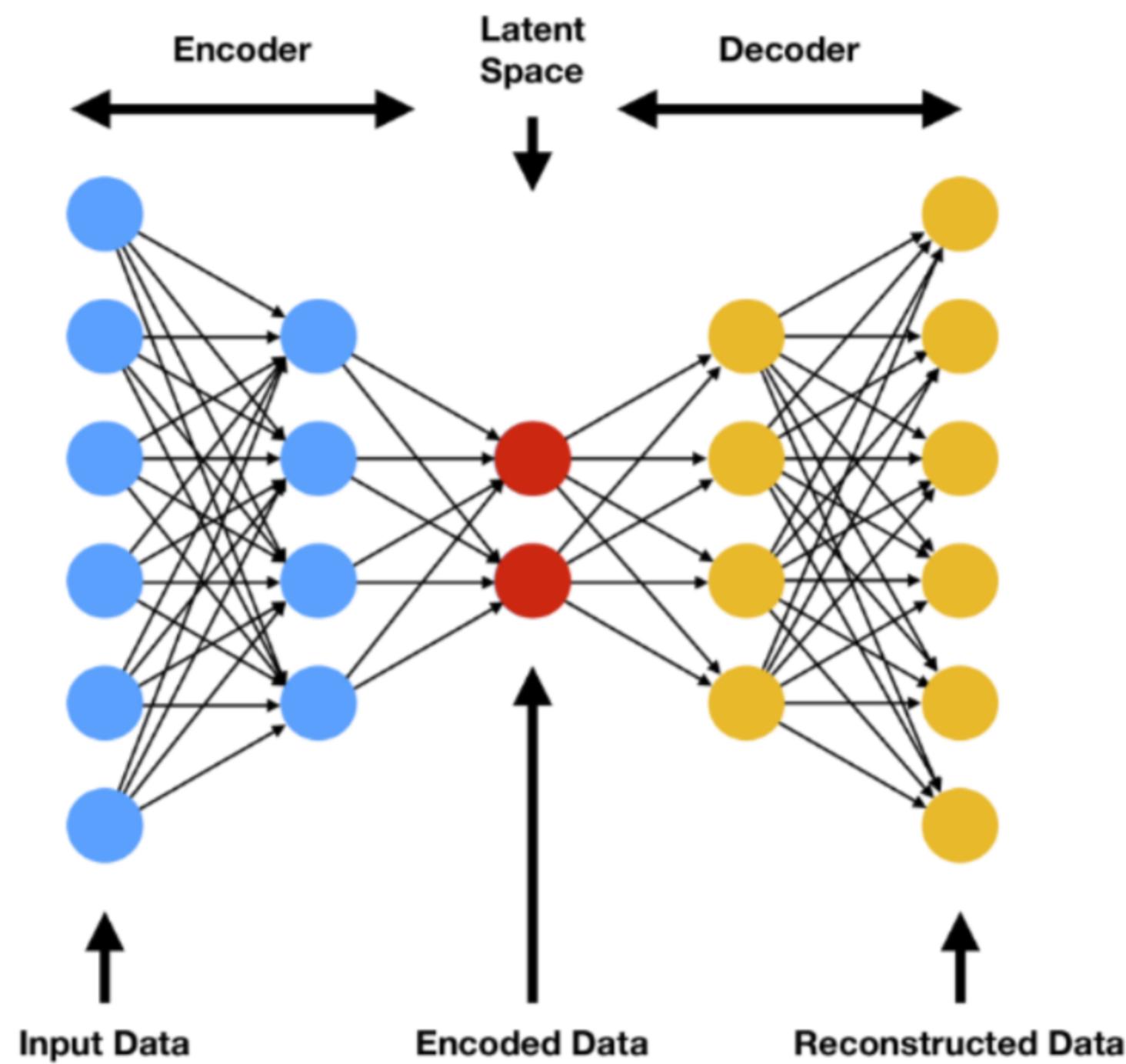


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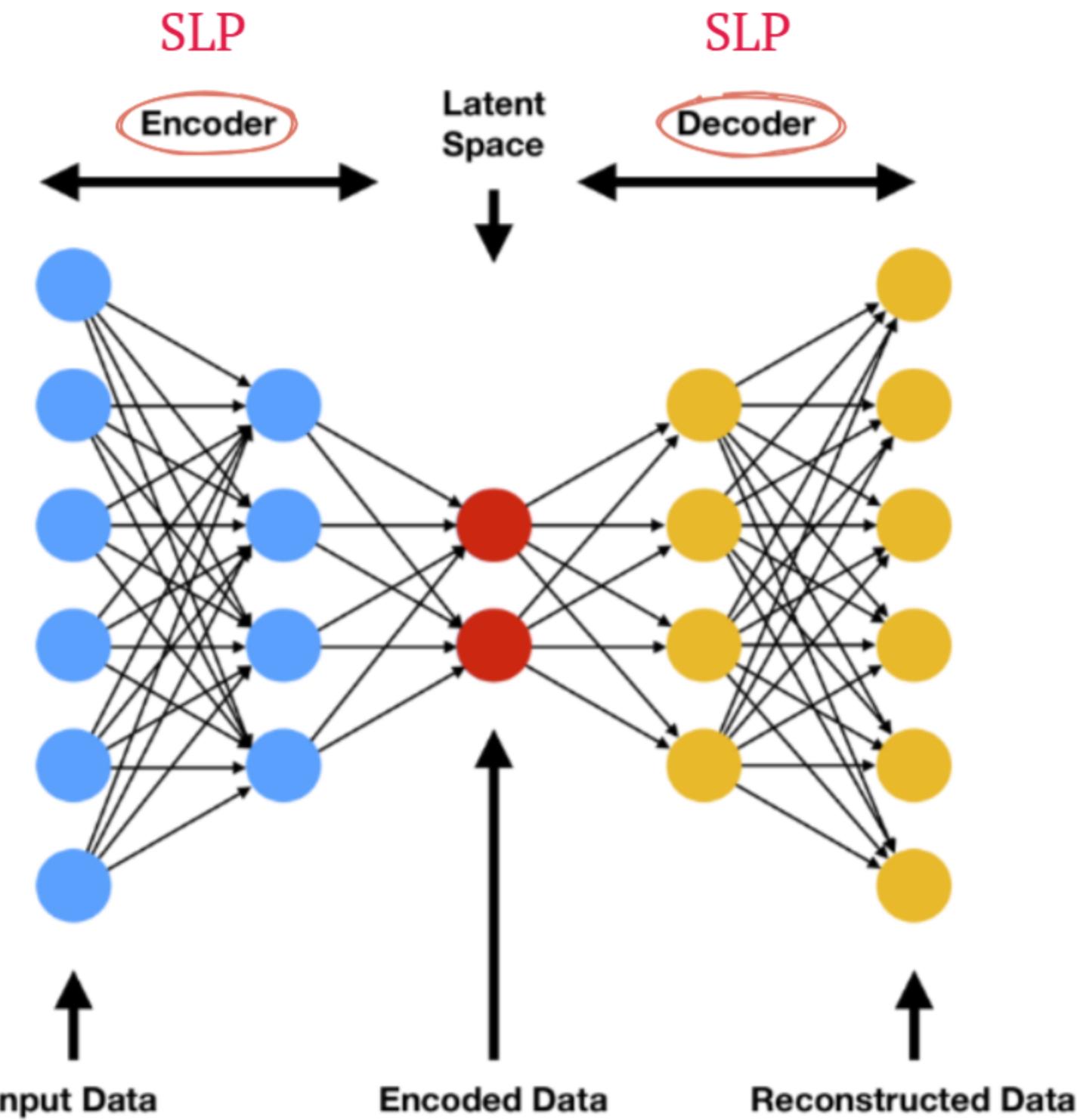
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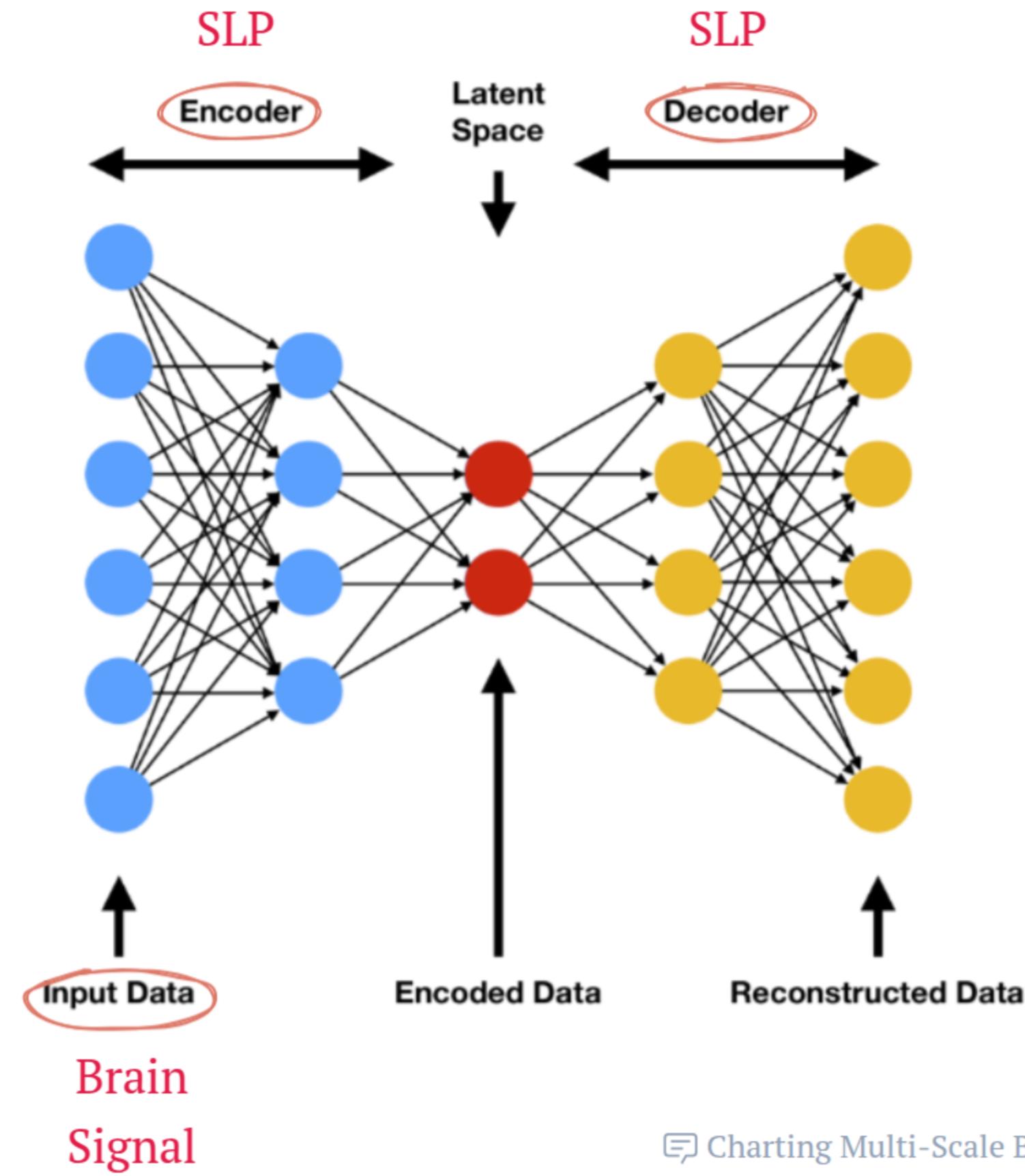
Conceptual analogy with autoencoders:



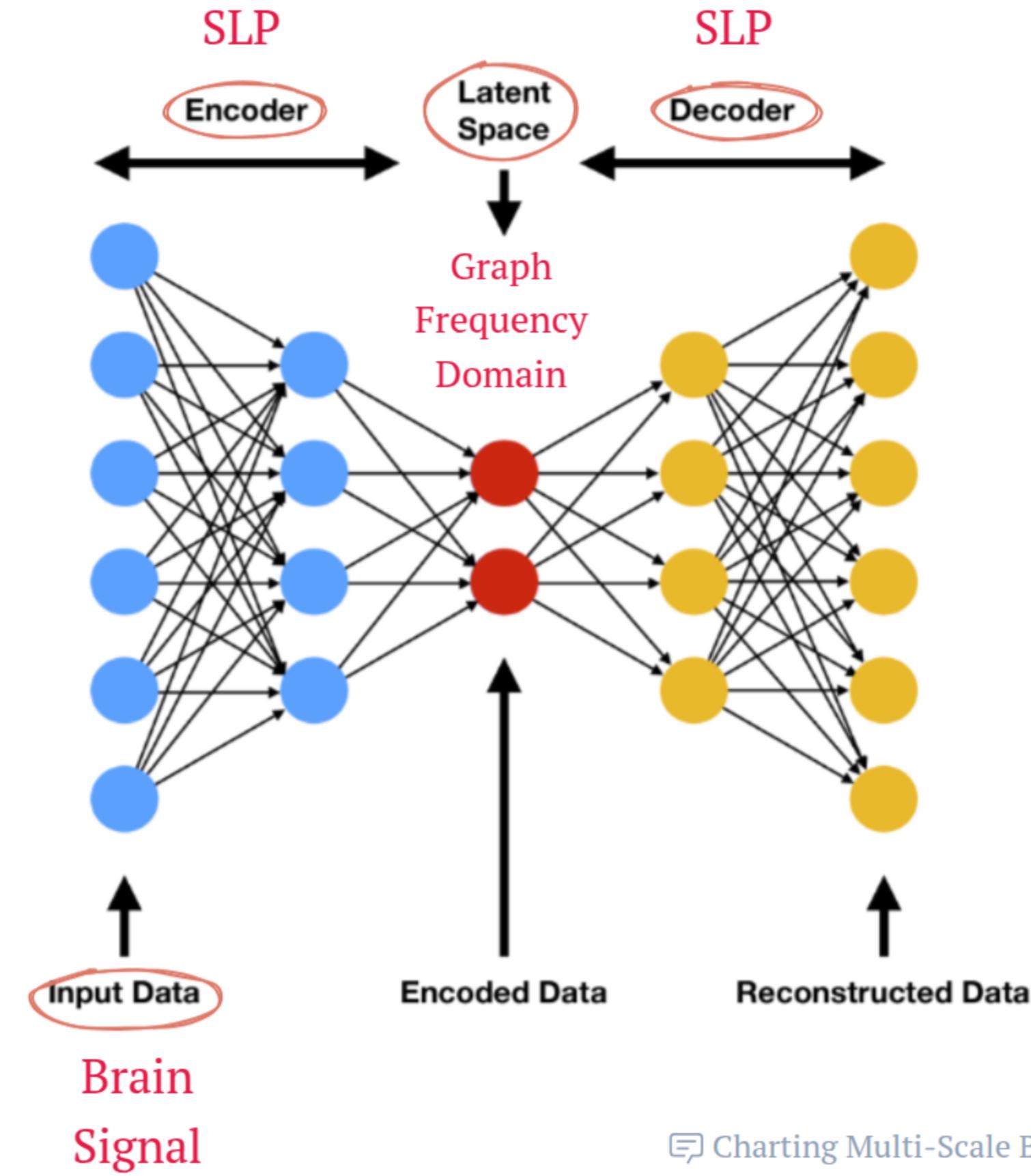
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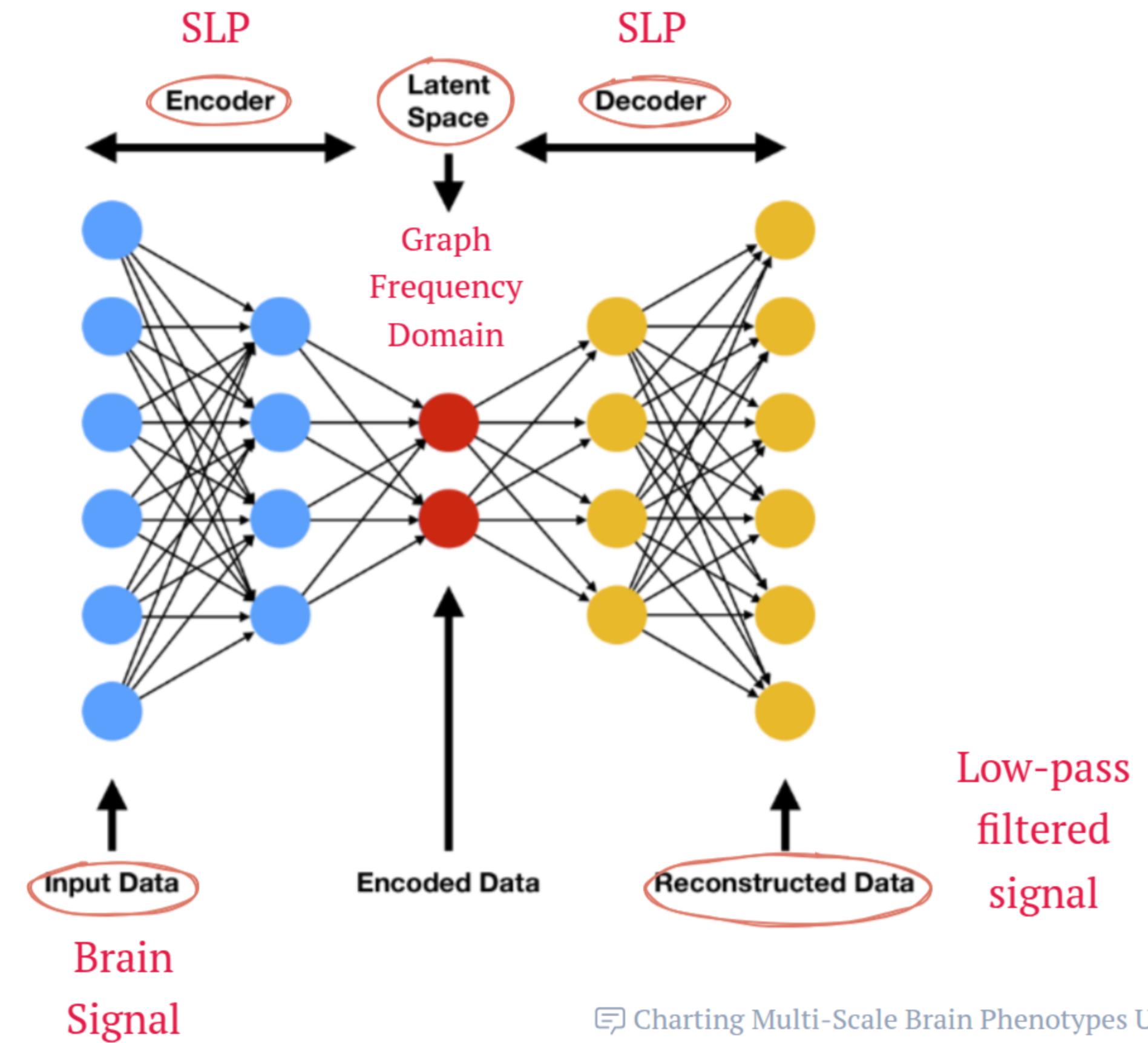
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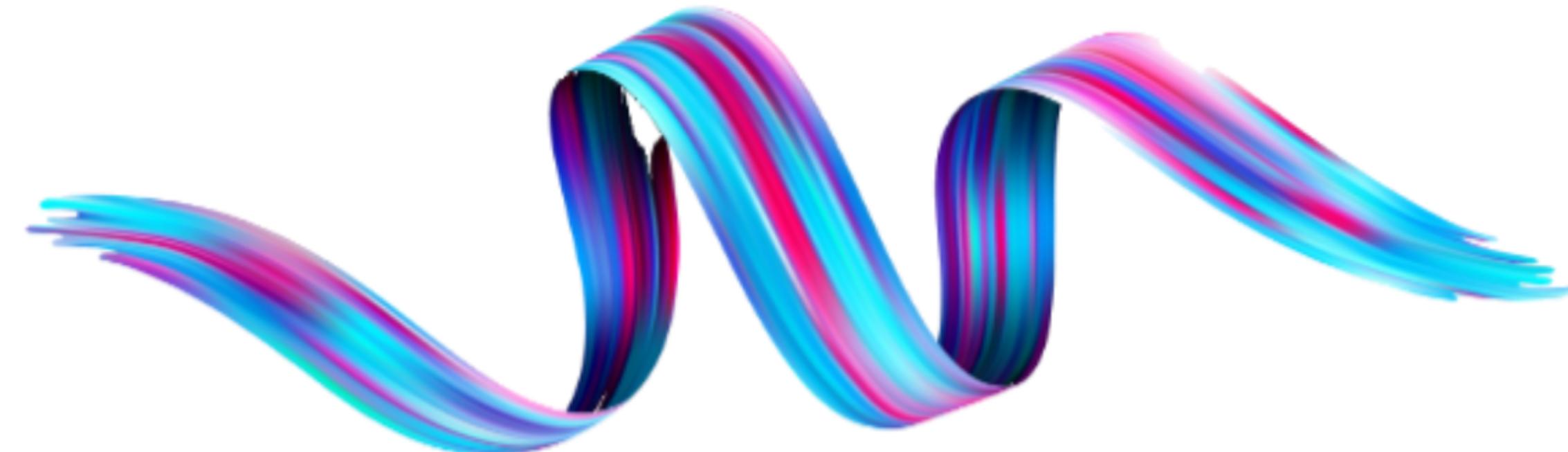
Spectral Normative Modeling

Spectral Normative Modeling

Bain
Eigenmodes

SNM

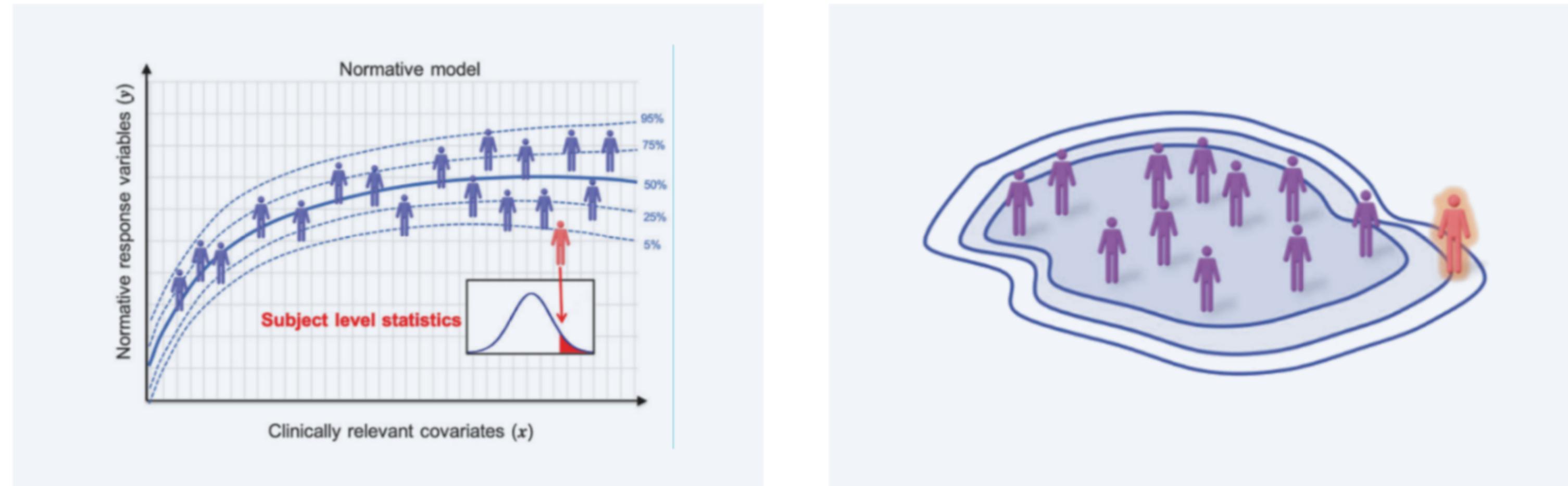
Normative
Modeling



Normative Modeling

Normative Modeling

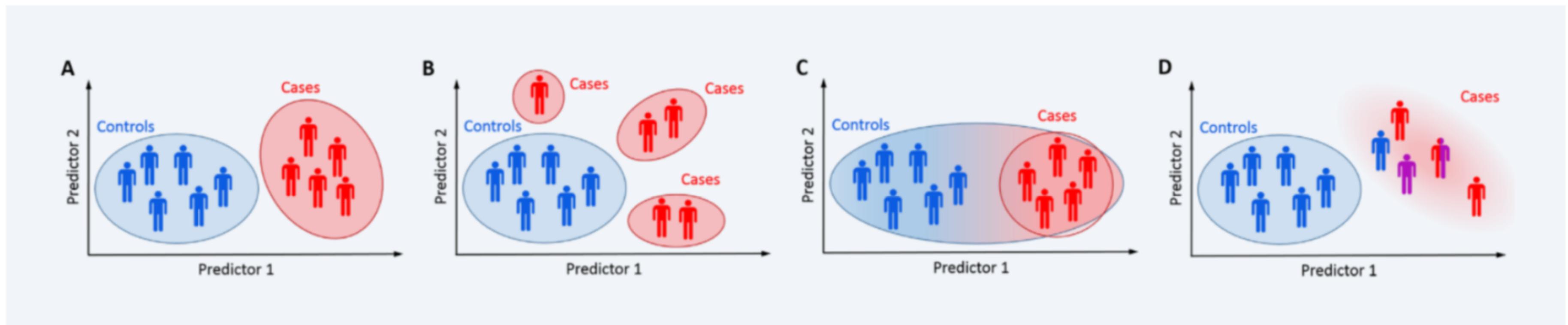
- Characterizes population-level phenotype distribution to detect individual deviations from the norm.



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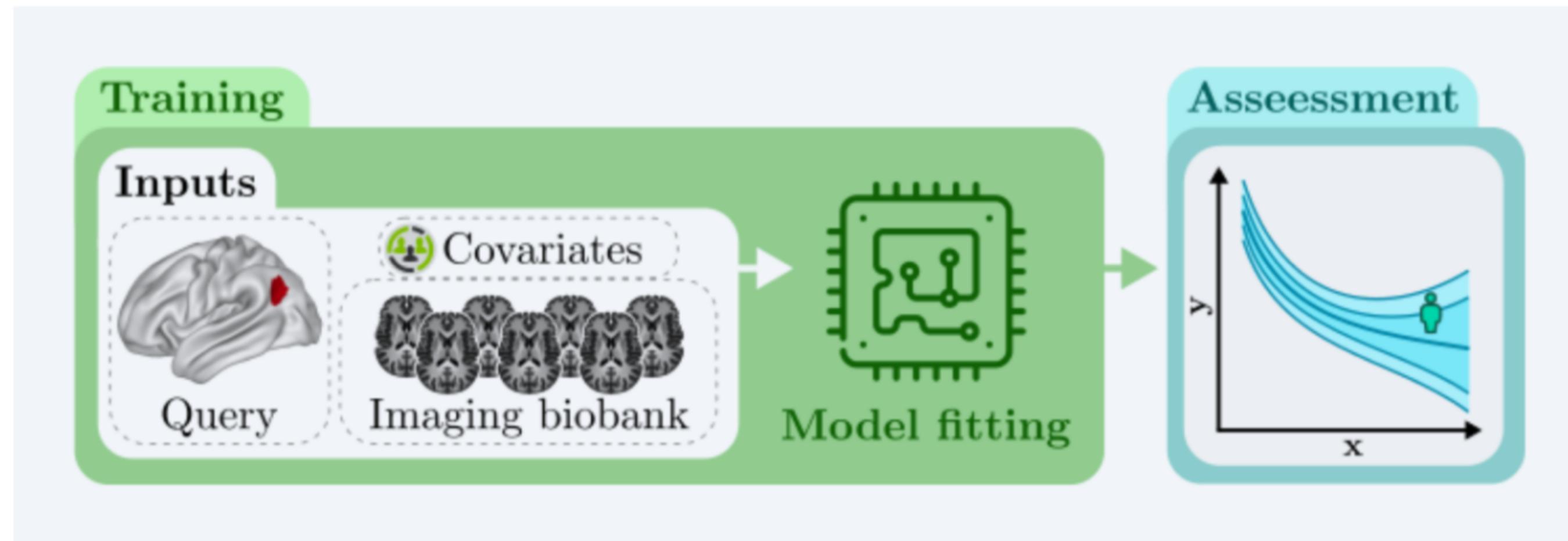
- Trained to infer normative ranges of a **predefined fixed phenotype (y)** from a set of covariates (X).

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

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)

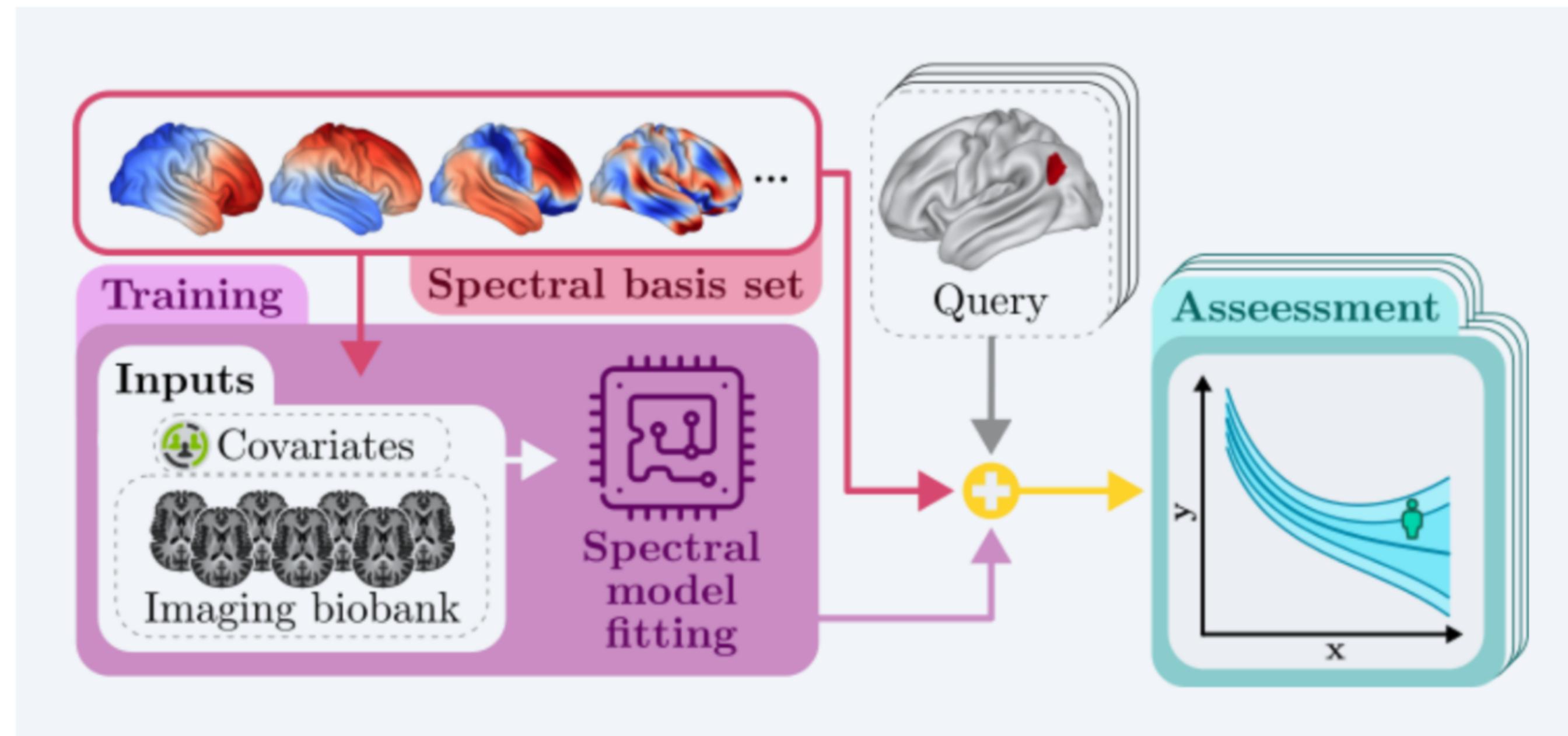
Spectral Normative Modeling (SNM)

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

Spectral Normative Modeling (SNM)

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

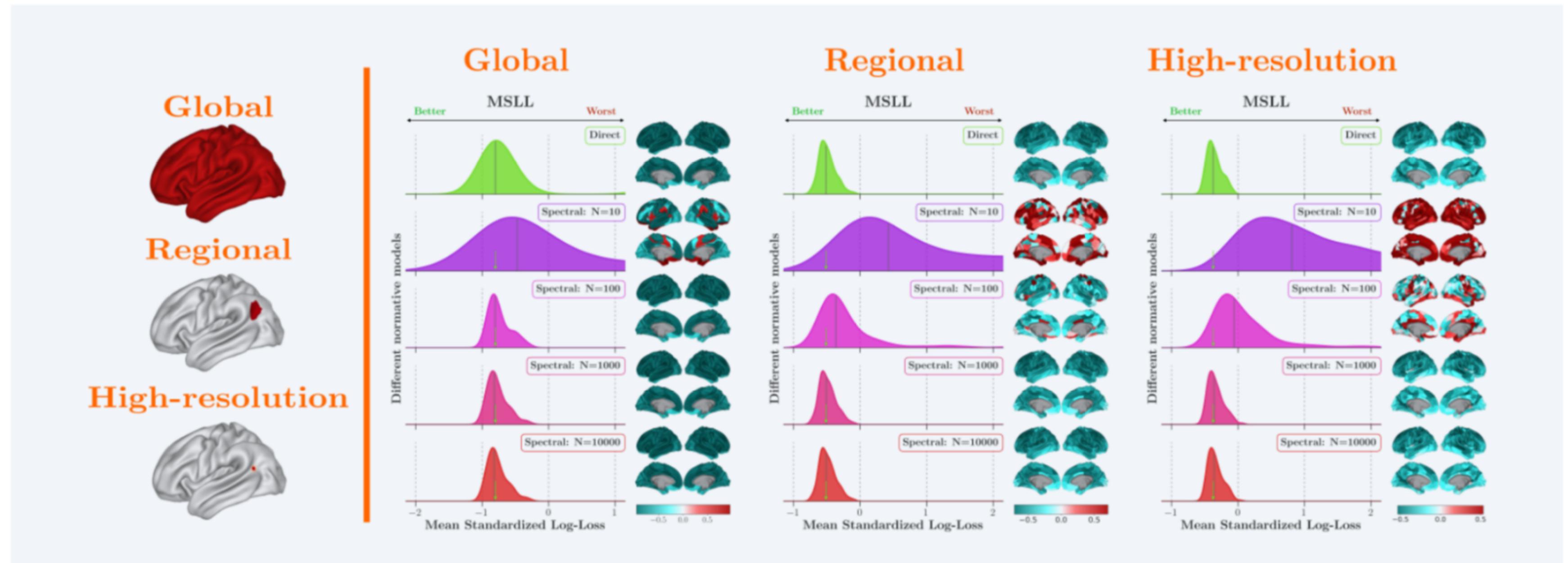


Mansour L. et al. (2025)

SNM performance

SNM performance

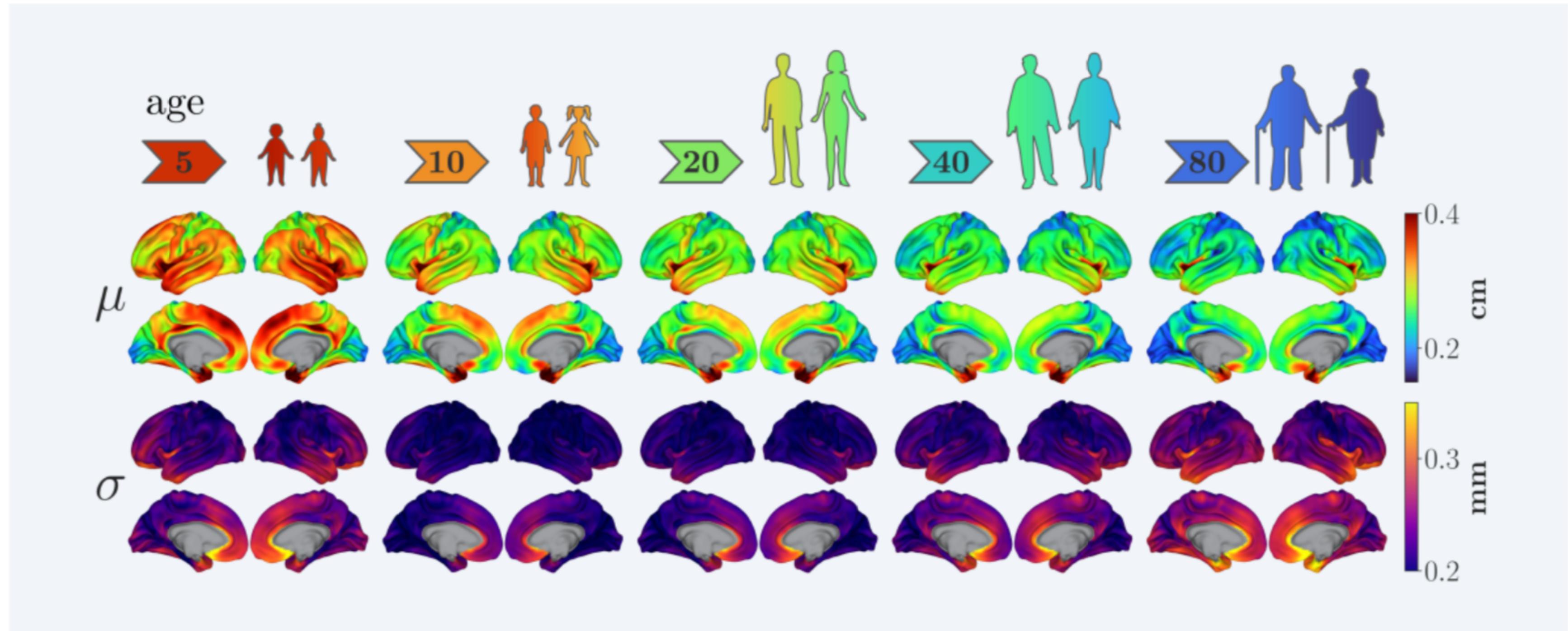
→ With at least **1000 modes** SNM achieves comparable estimates to that of a direct model.



High-resolution normative modeling

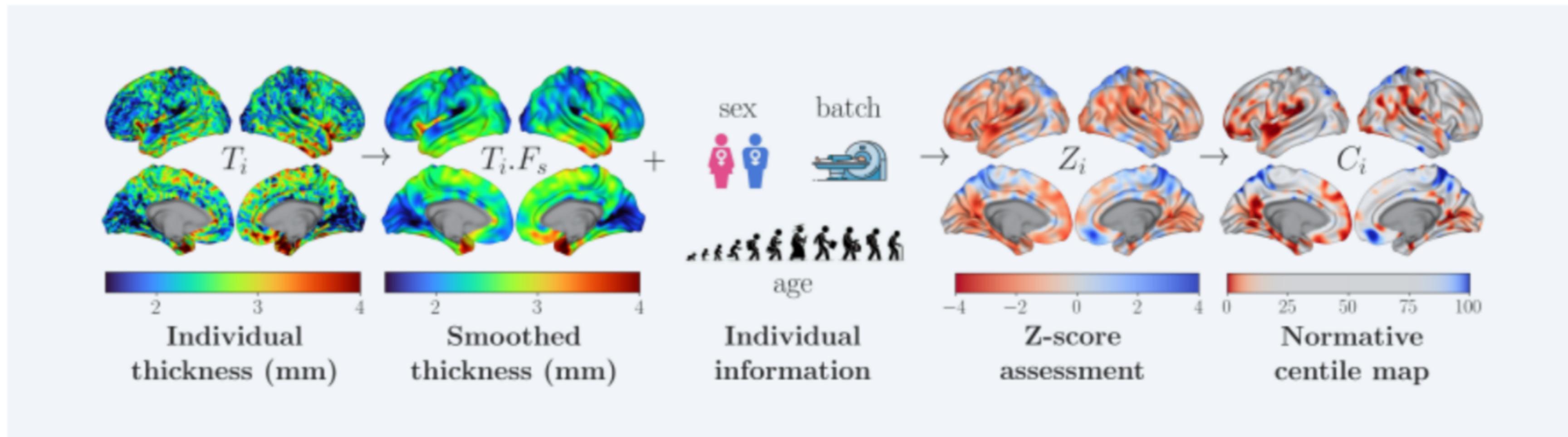
High-resolution normative modeling

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



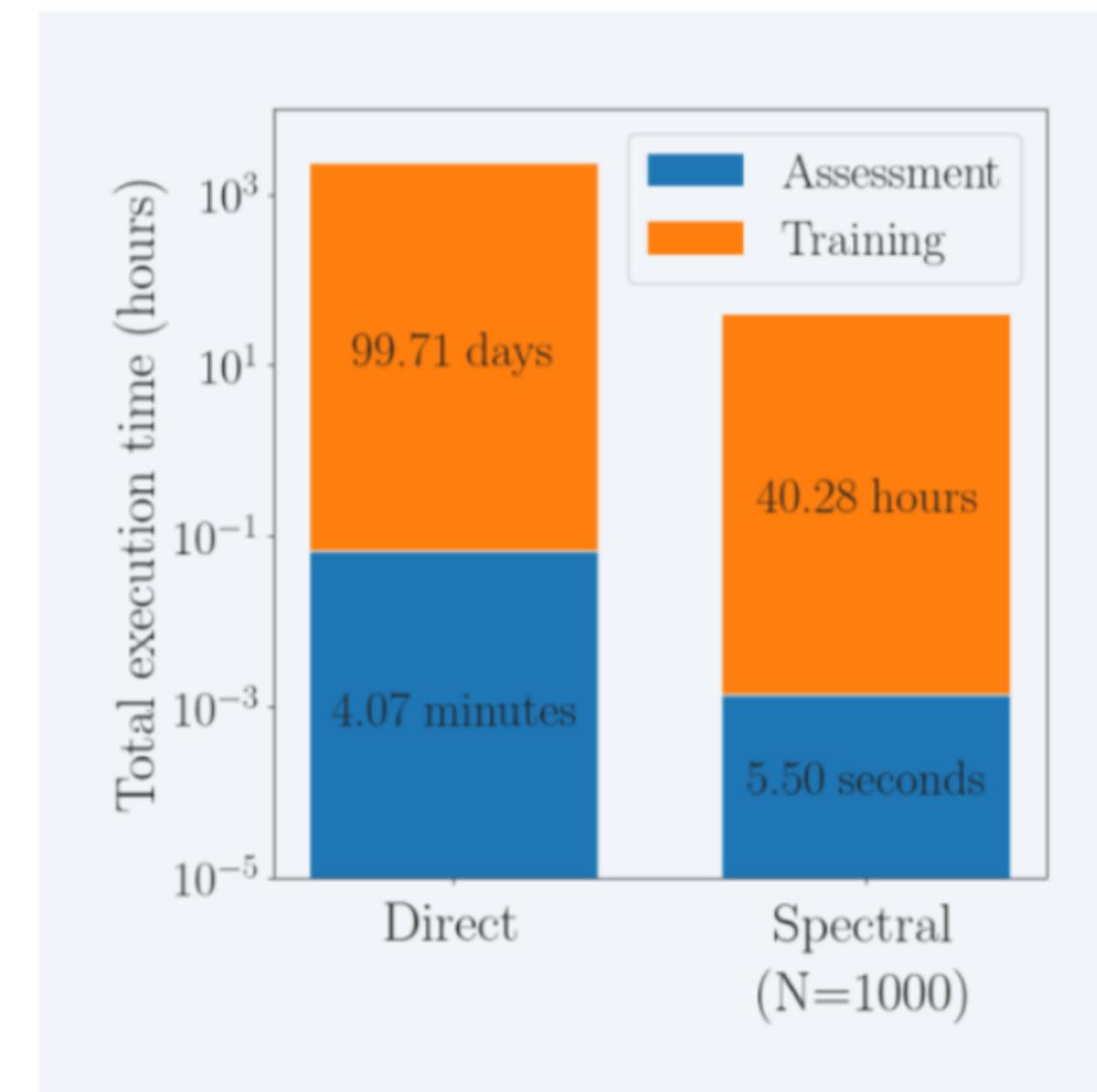
High-resolution normative modeling

- 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)

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

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

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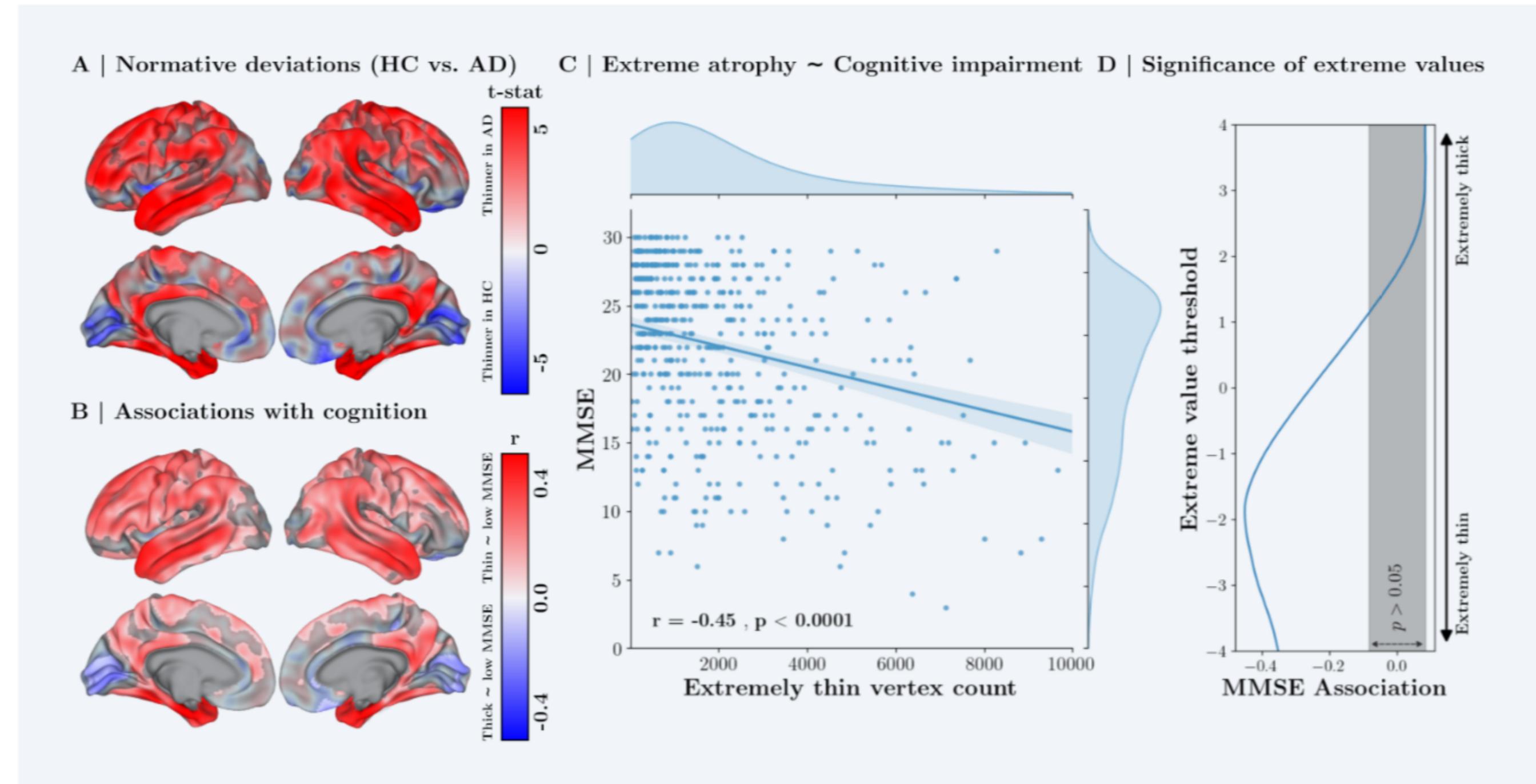
Train SNM on a healthy normative sample (HCP Lifespan)

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

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

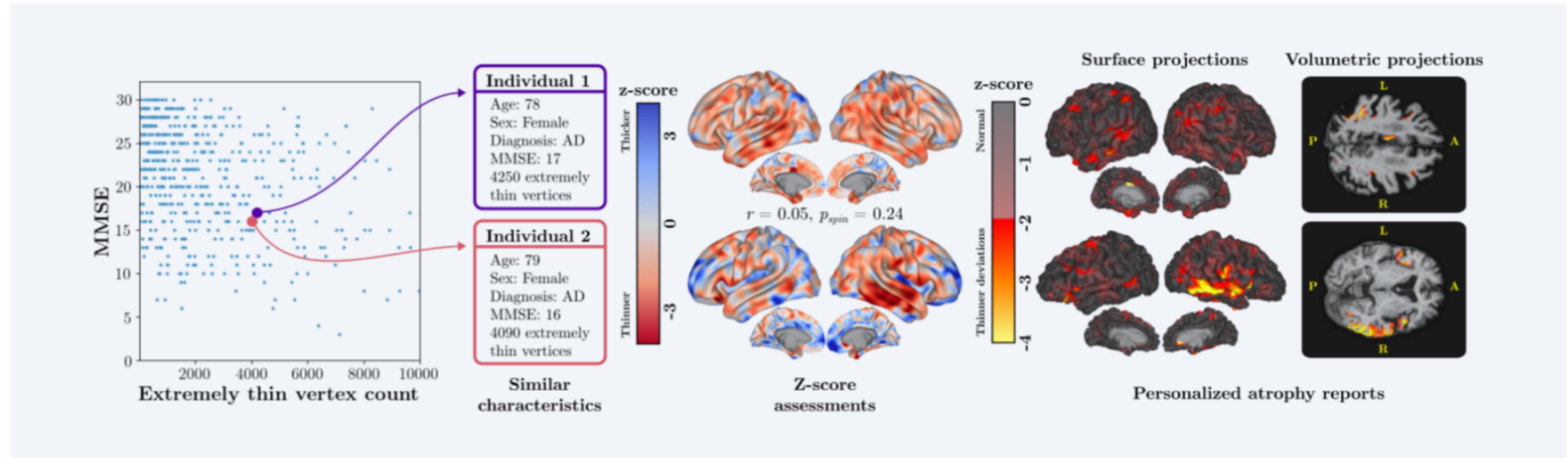
Clinical application: AD dementia

→ Population-level evaluations: Cortical correlates of cognitive decline



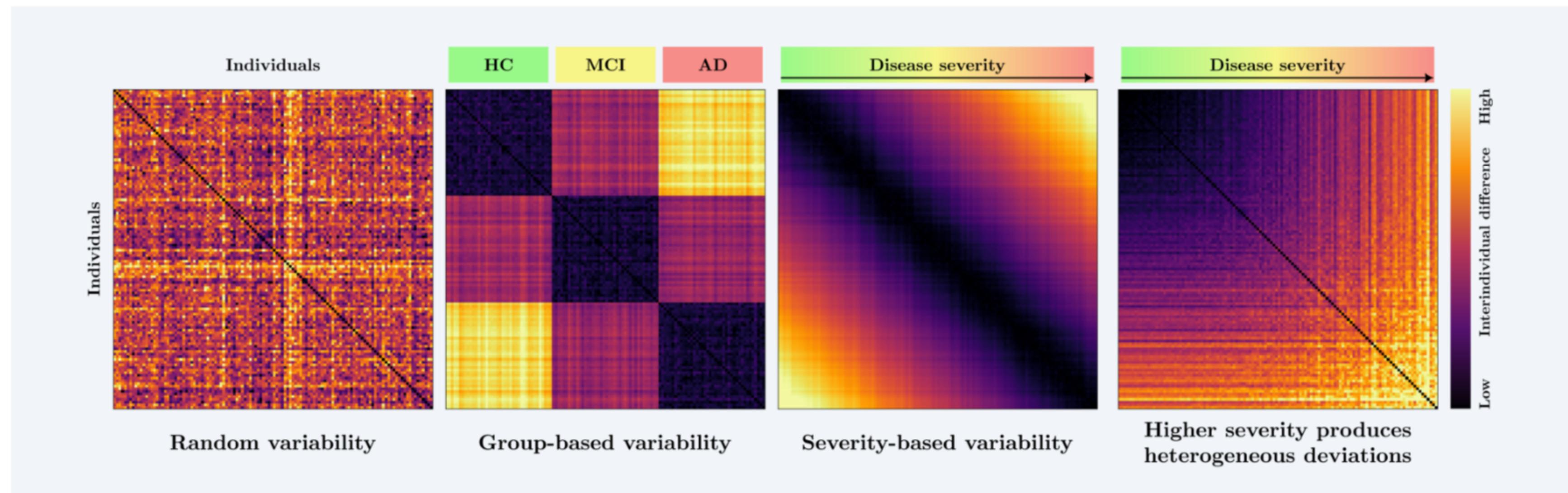
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→ Individual-level evaluations: Heterogeneous landscape of dementia-induced cortical atrophy



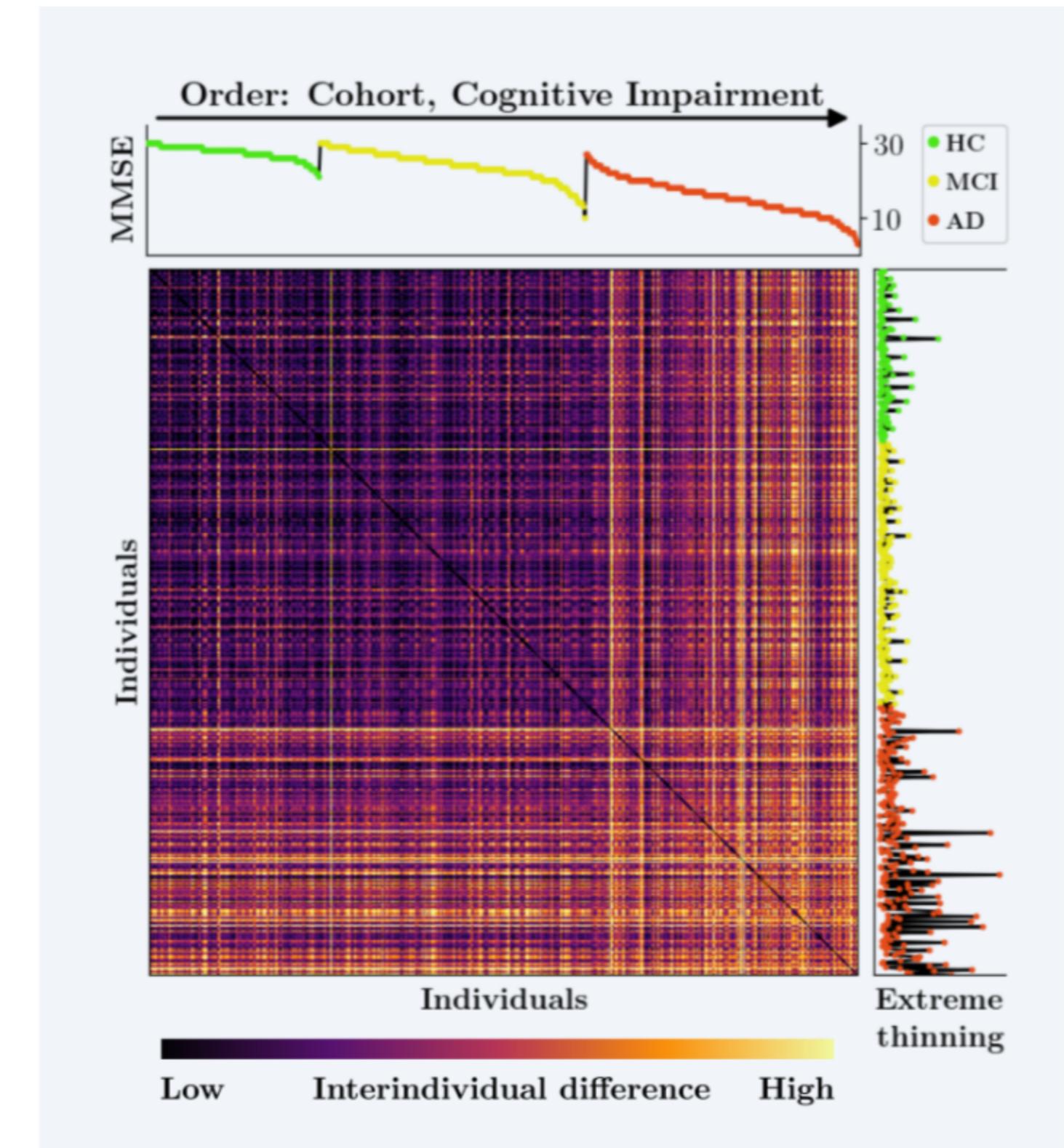
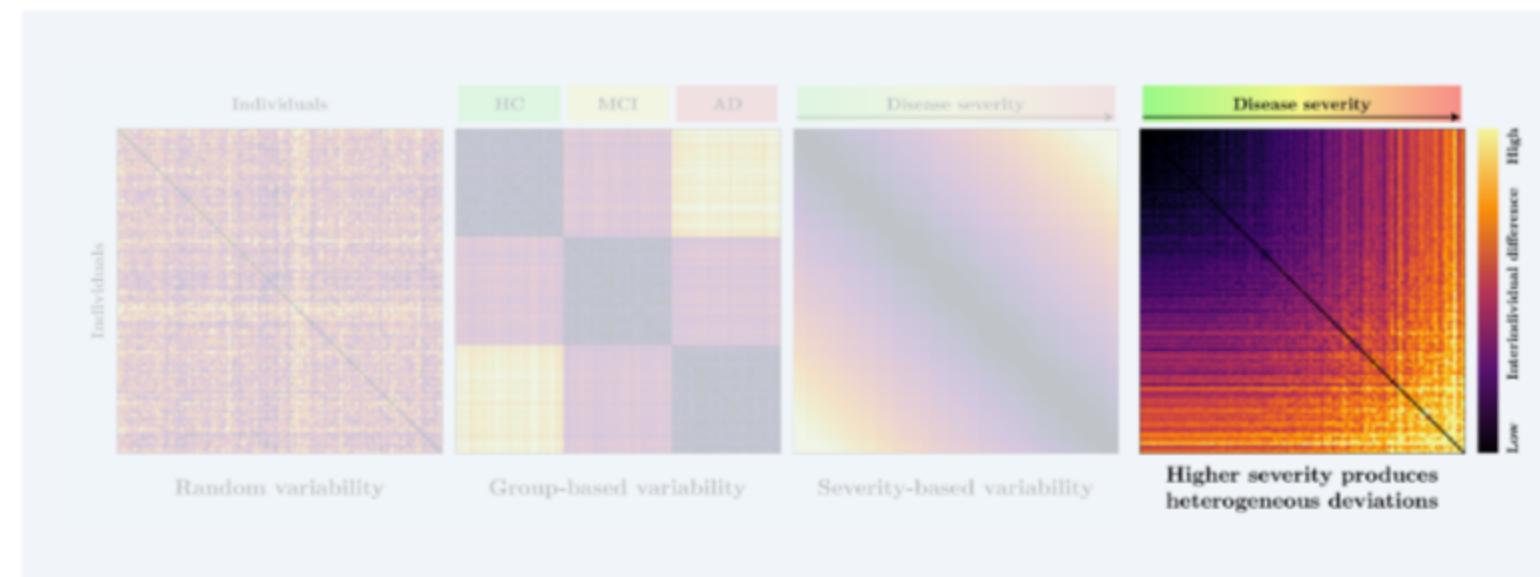
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→ Hypothetical patterns of interindividual variability



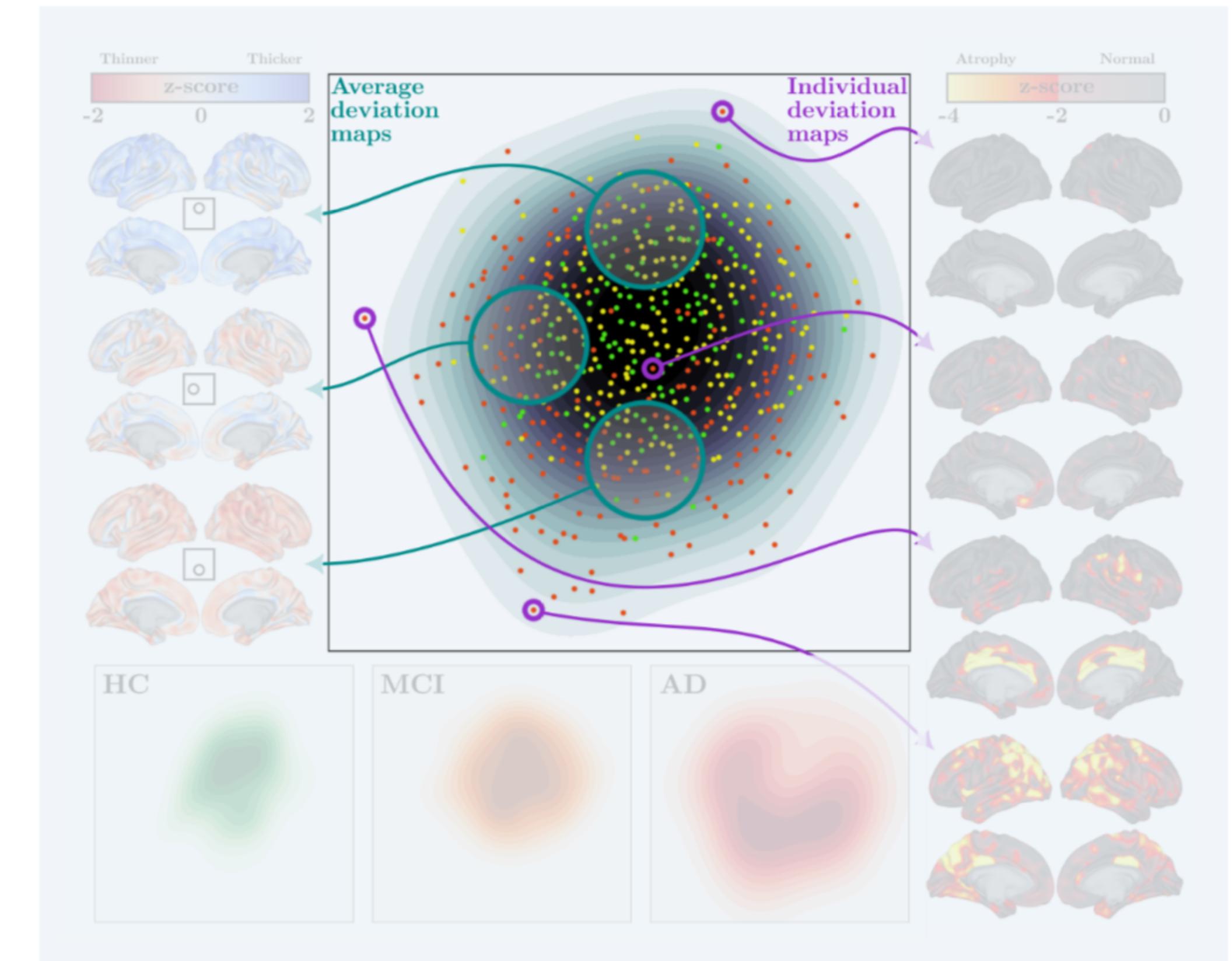
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→ Empirical variability



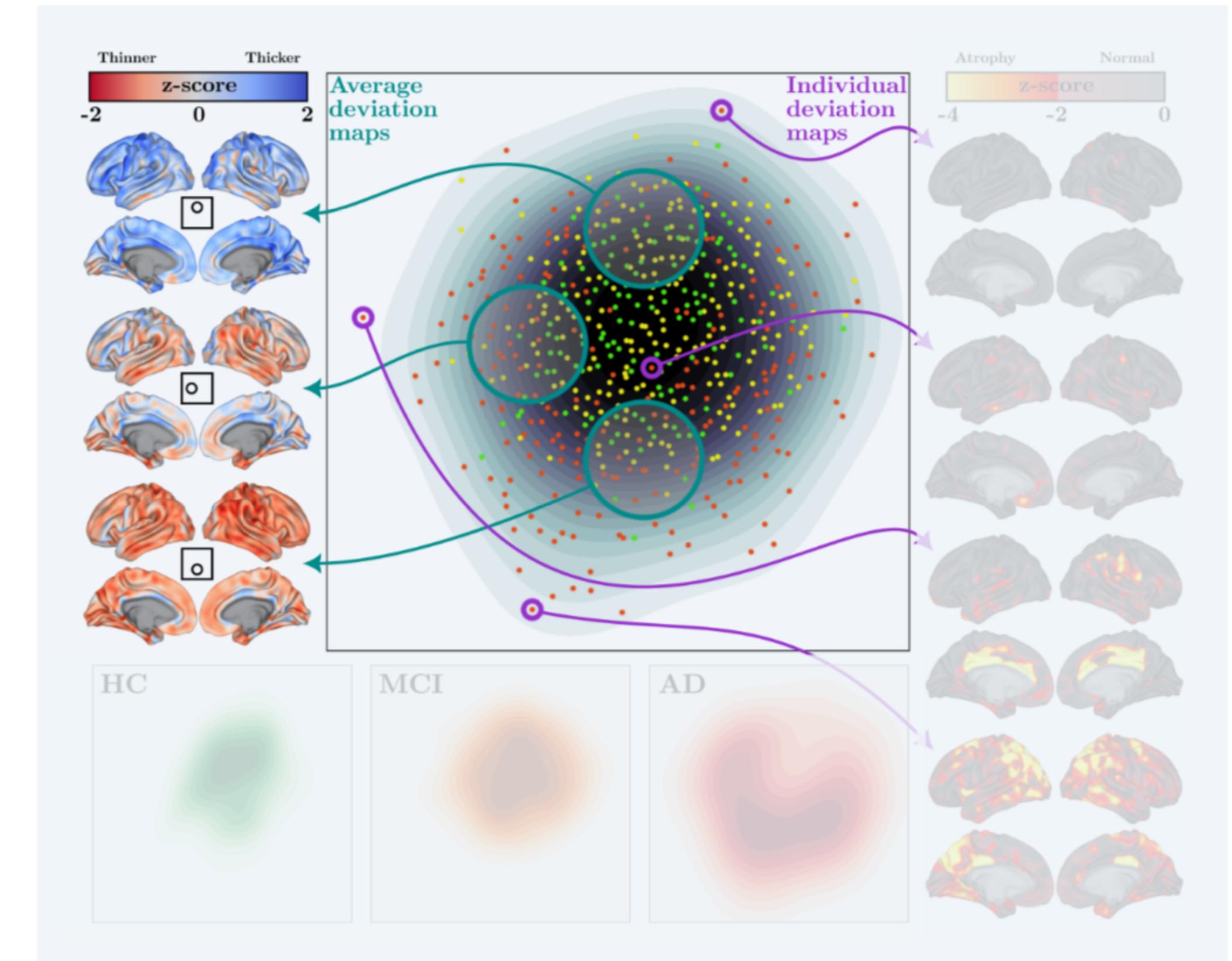
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→ Individual heterogeneity



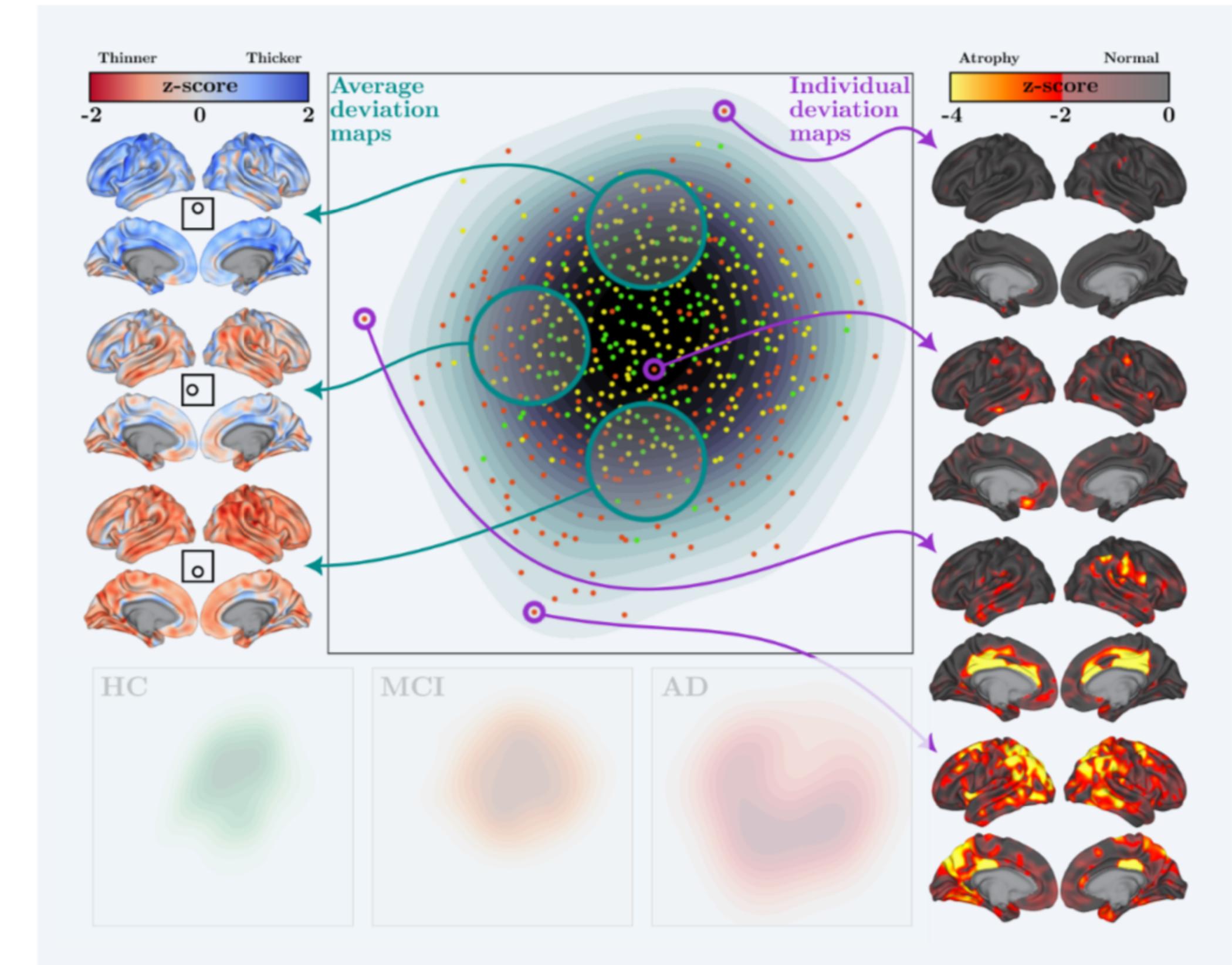
Clinical application: AD dementia

→ Individual heterogeneity



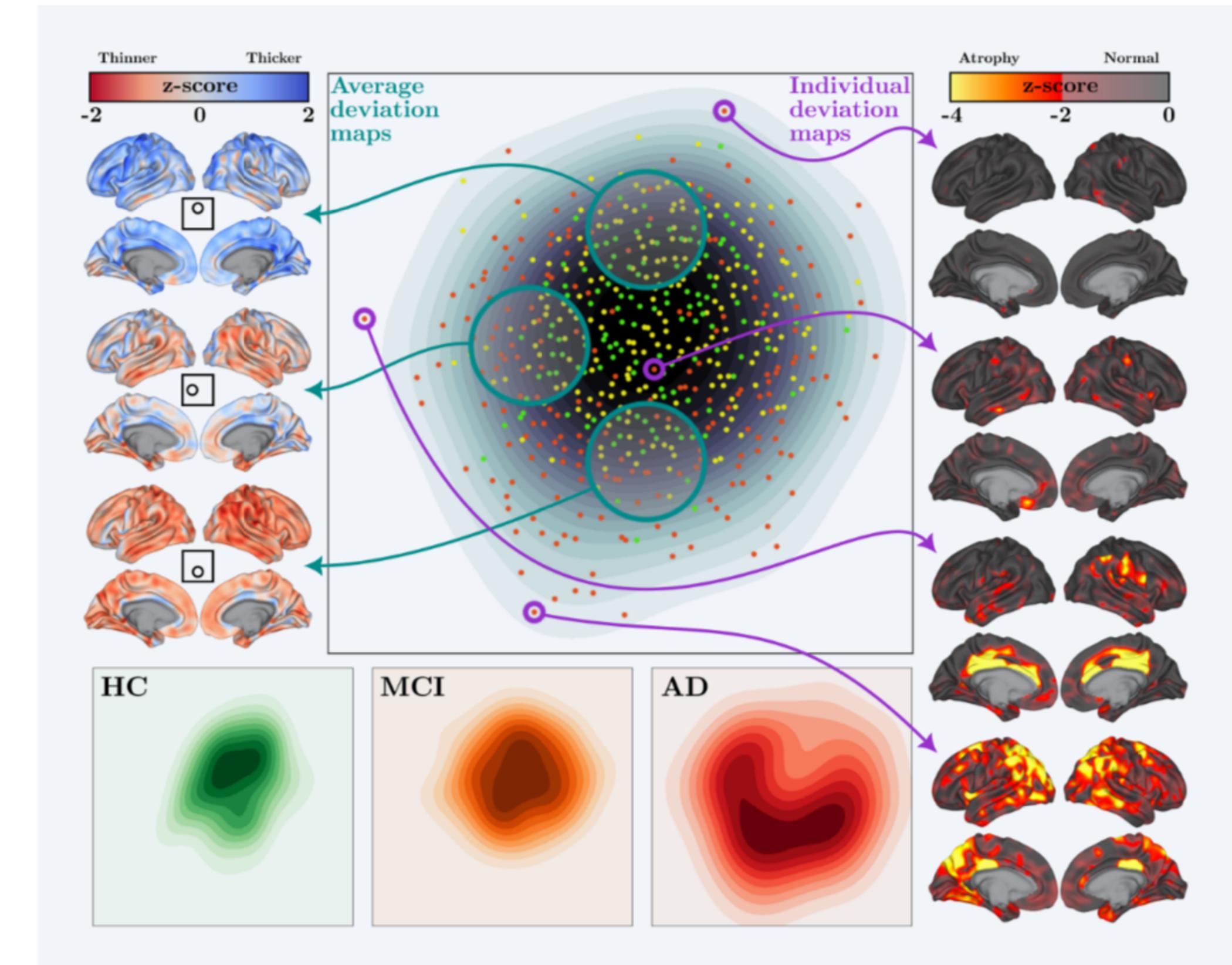
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→ Individual heterogeneity

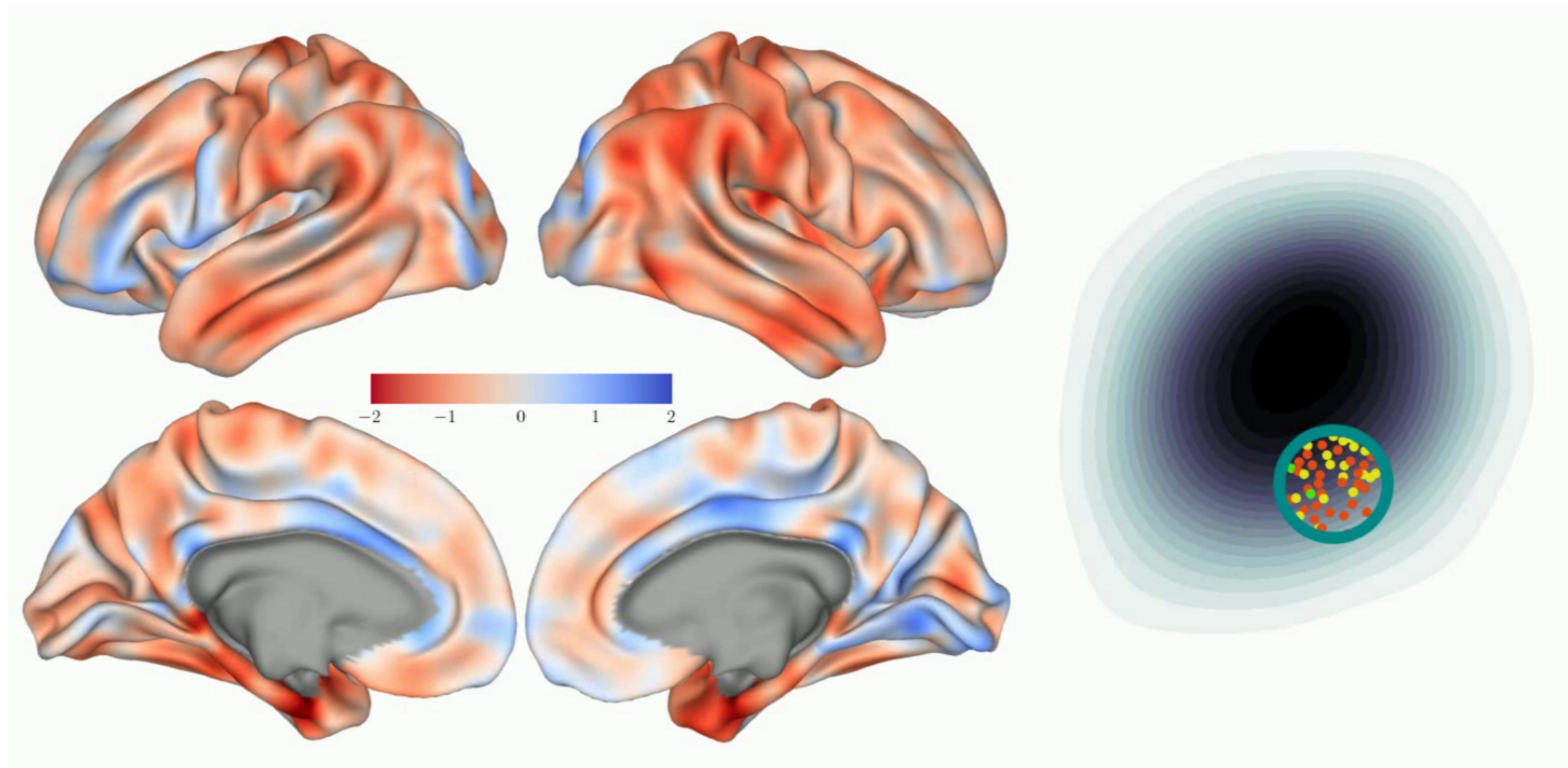


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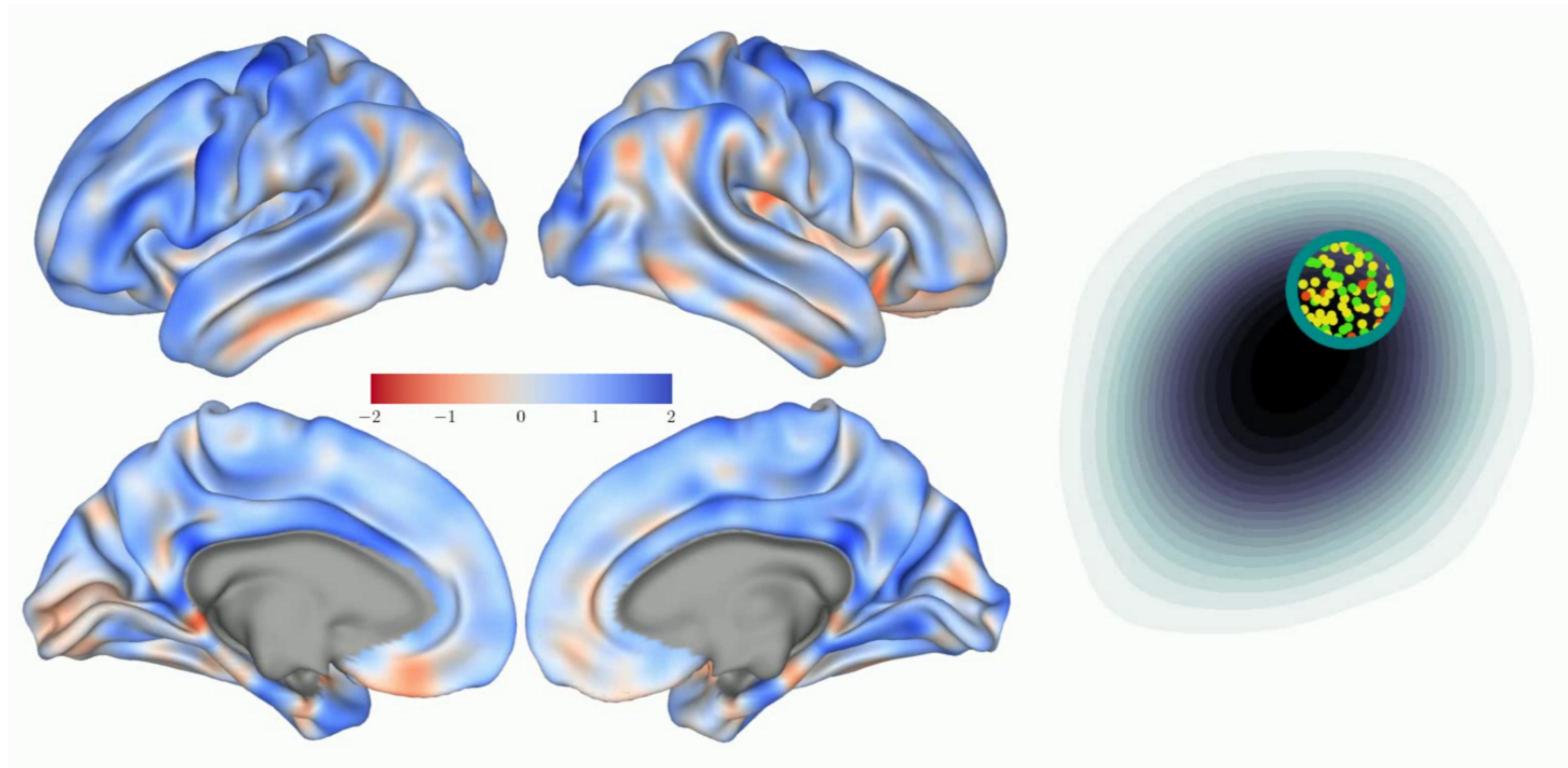
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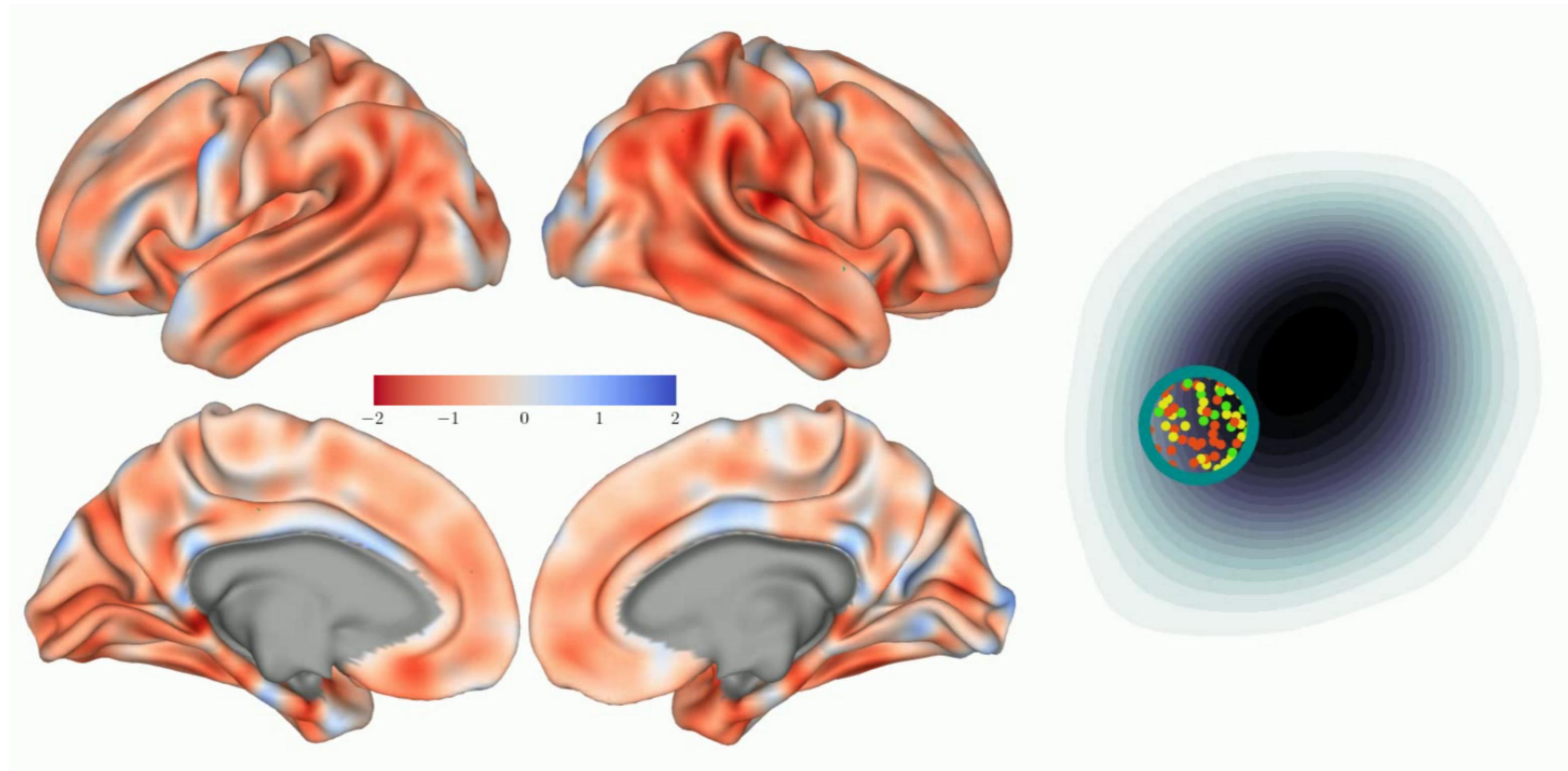
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Concluding remarks

Future Directions

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These techniques facilitate processing big data in neuroimaging datasets.

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

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MELBOURNE



NUS

National University
of Singapore

Charting Multi-Scale Brain Phenotypes Using **Spectral Normative Models**

Presentation slides for the ISMRM Workshop on 40 Years of Diffusion



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