

# Human Brain Normative Modeling Using Eigenmodes

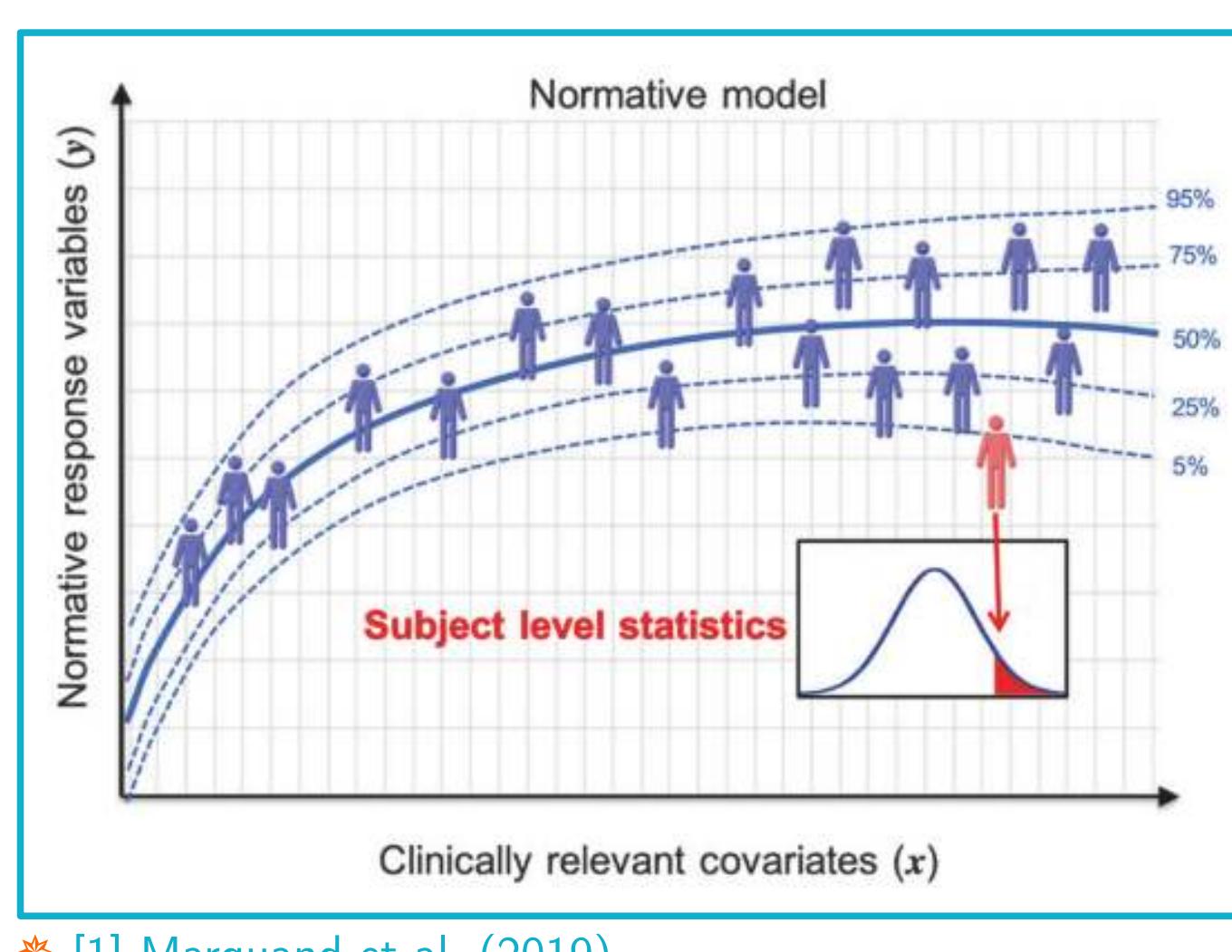


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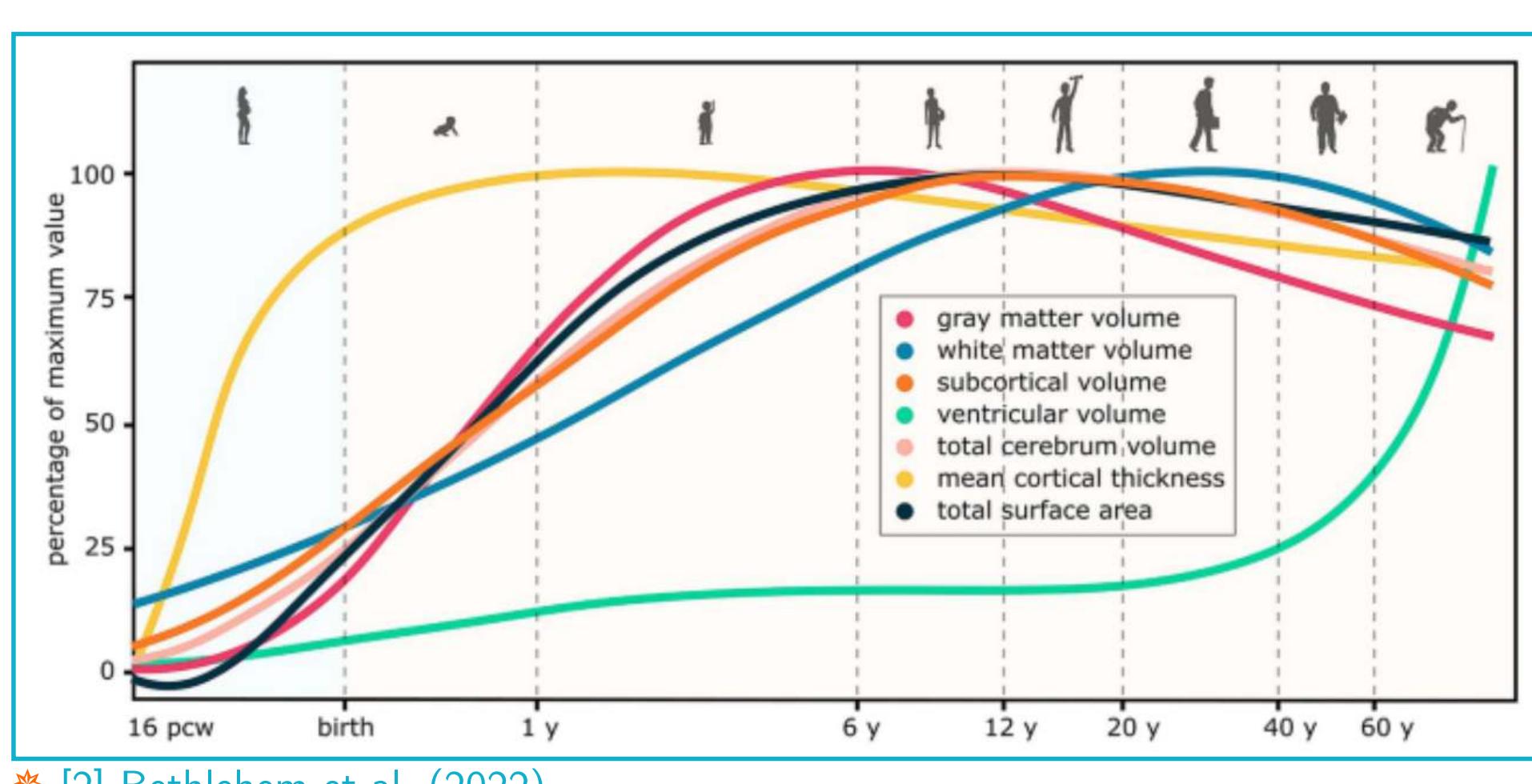
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## Introduction

Normative models (NMs) construct reference charts for population-wide distributions of a biological phenotype. Similar to growth charts assessing a child's height based on their age and sex, normative brain charting is a framework for modeling variations in structural brain phenotypes, such as cortical thickness. Previous research has demonstrated NM's efficacy in accurately capturing the heterogeneity of normative deviations in brain structure [1].



Normative charting of brain MRI data holds the potential to yield insightful spatial estimates of variations in cortical phenotypes [2]. Nevertheless, methodological limitations have thus far impeded the development of NMs with high spatial precision [3].



The establishment of a normative framework to detect **subtle spatial nuances** remains an unfulfilled aspiration for precision psychiatry.

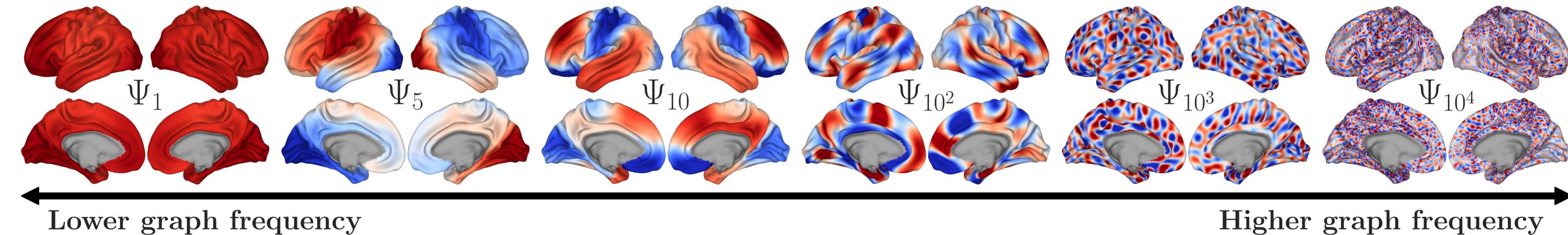
## Methods

To establish and evaluate our normative reference models, we combined data from three distinct **Human Connectome Project (HCP)** cohorts to cover the human lifespan (HCP Development, Young Adult, and Aging), comprising 2,473 individuals (54.7% female) aged 5 to 100. Cortical thickness was used as the normative phenotype of interest.

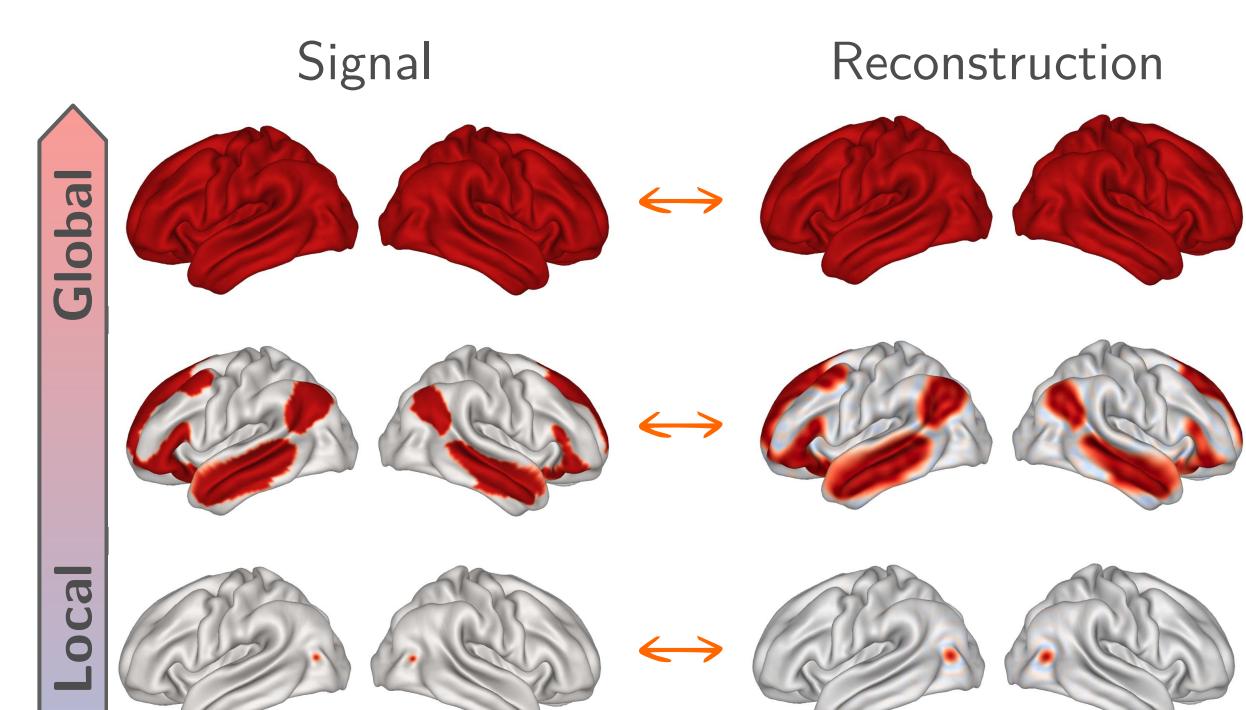


Computing **high-resolution NMs** is challenging due to the dimensionality of the feature space (thousands of vertices on the surface mesh). Low-dimensional encoding of cortical phenotypes can enable the development of computationally tractable high-resolution NMs. To this end, we utilized brain **eigenmodes** [4] as basis functions for information reconstruction.

### Brain eigenmodes



Eigenmodes were utilized as basis for normative reconstruction via graph signal filtering [5].

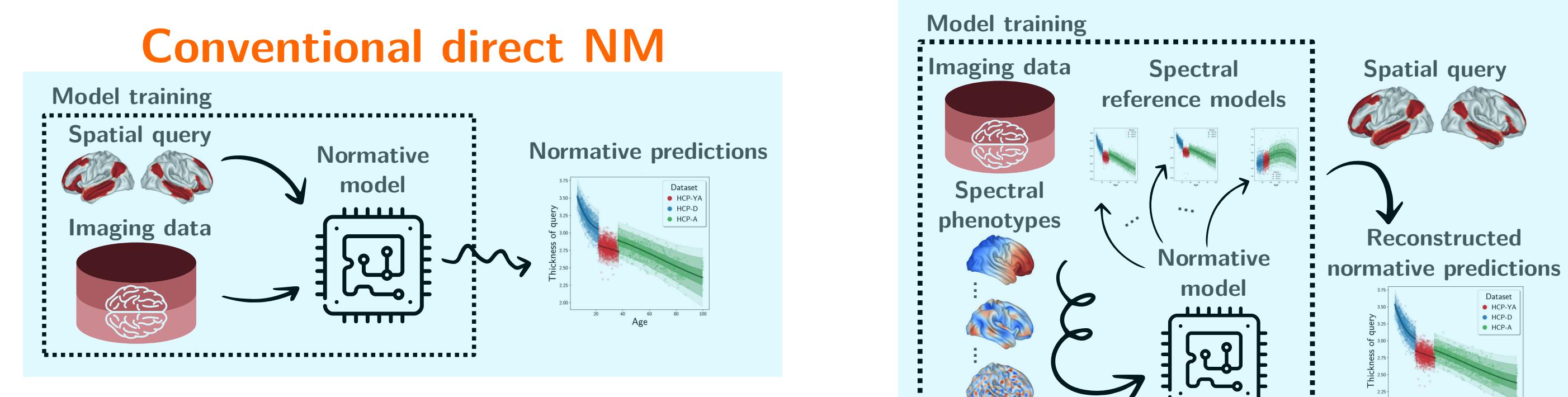


Thickness loading on each eigenmode formed a distinct spectral phenotype of the cohort. Separate hierarchical Bayesian regression NMs were trained to independently model spectral cortical thickness phenotypes as a function of age and sex while accounting for scanner/site effects. This facilitated the generalization of pre-trained reference NMs to unseen spatial normative queries.

## Results

Spectral vs. conventional (direct) normative modeling:

### Spectral NM

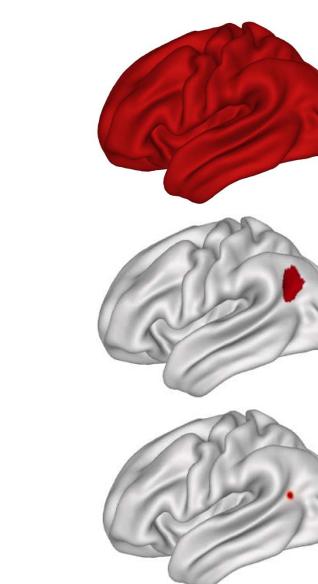


Spectral NM eradicates the necessity for retraining the model when encountering new queries, thus removing the requirement for repeated processing of imaging data to gain novel normative insights.

After training spectral NMs, we conducted a comprehensive evaluation of their ability to infer norms in comparison to a direct model.

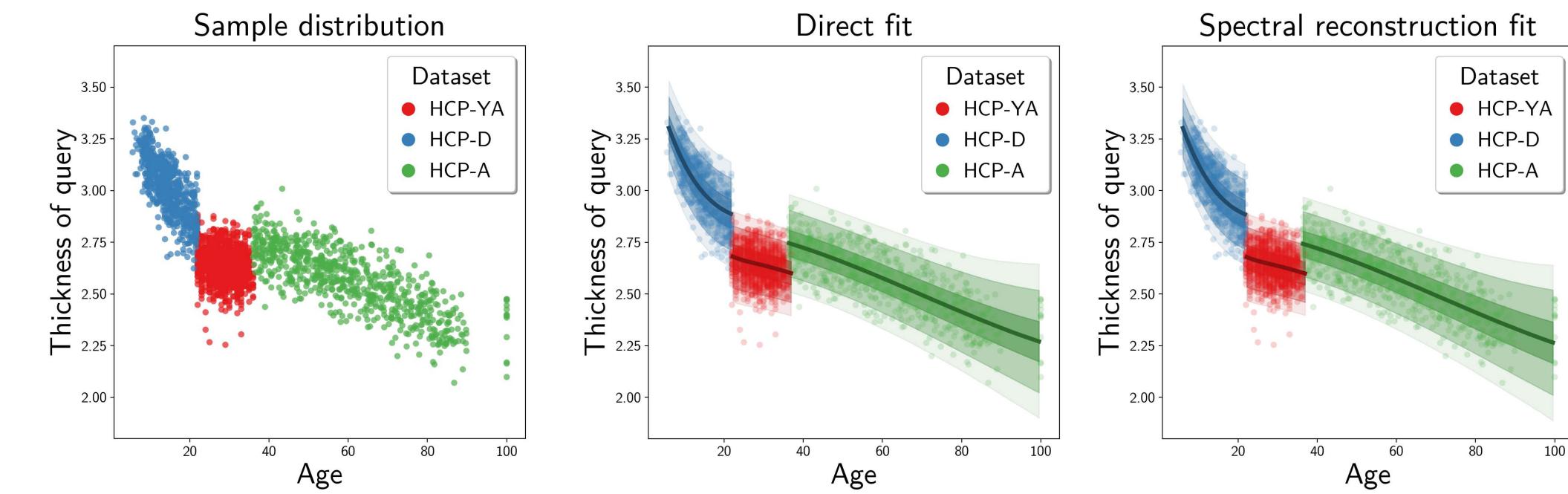
Three alternative families of spatial queries were tested:

- Global spatial queries  
(e.g., total mean thickness)
- Regional spatial queries  
(e.g., mean thickness of a parcel)
- High-resolution queries  
(focused on a specific cortical vertex)

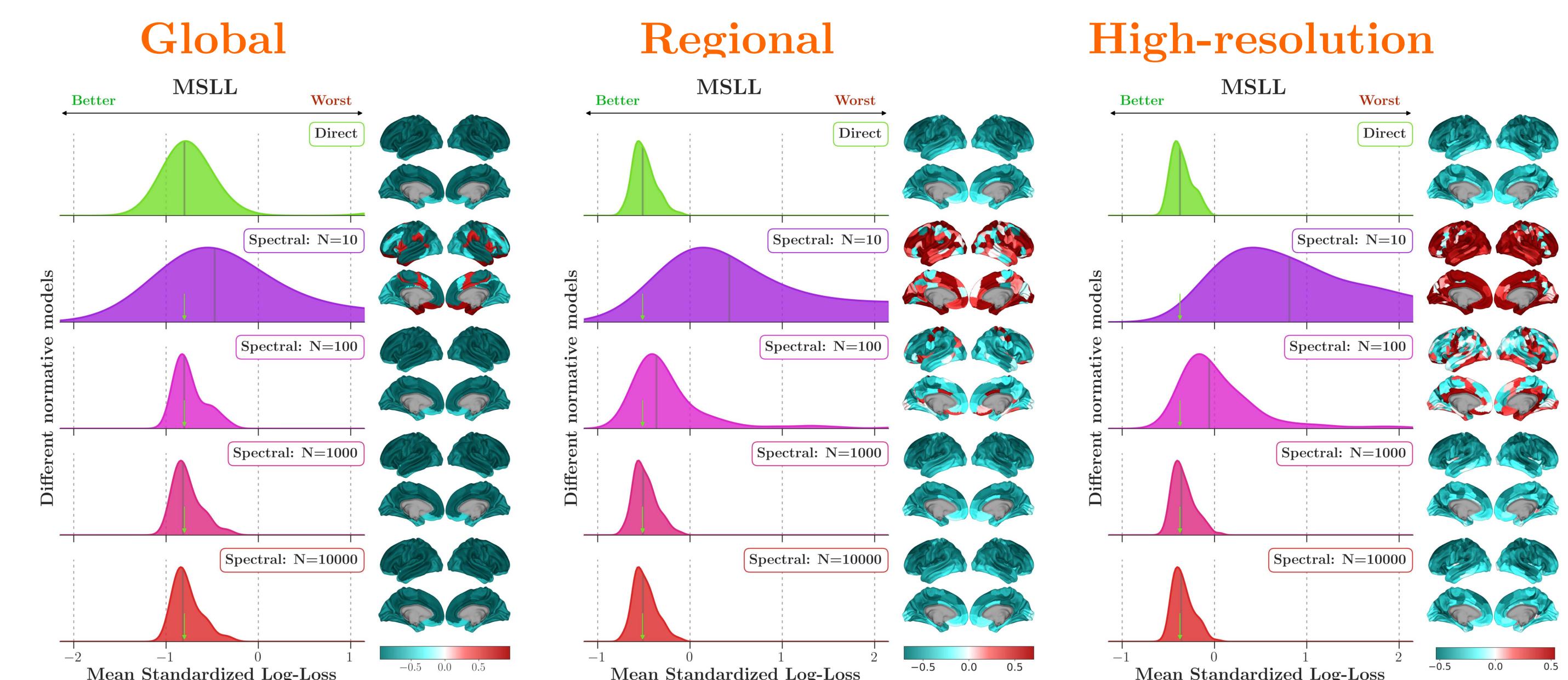


Spectral NMs can generate effective normative ranges at various spatial resolutions.

### Visual comparison:



### Quantitative evaluations:



## Concluding remarks

We present a novel approach for high-resolution normative modeling via pre-trained spectral NMs constructed from brain eigenmodes. Spectral NMs can accurately estimate normative ranges. Obviates the necessity to fit separate models for distinct spatial queries. Opens new avenues for precision lifespan human brain charting.

