

Spectral Normative Modeling (SNM) for High-Resolution Brain Abnormality Inference



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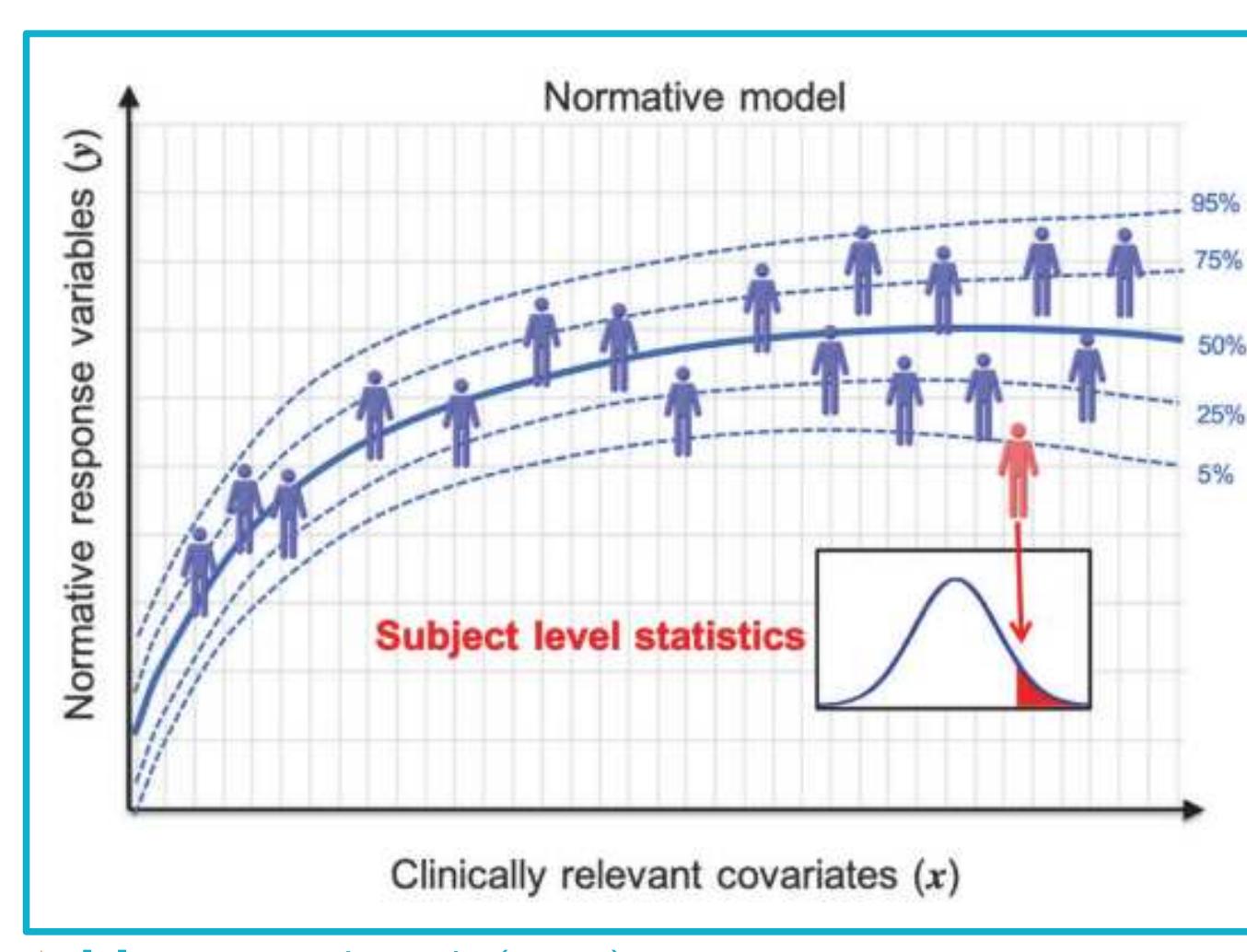
Affiliations are listed in the online version (scan QR code).

Introduction

Normative models (NMs) establish reference charts to characterize interindividual variability in a biological phenotype. Similar to pediatric growth charts assessing a child's growth based on 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 exploring the heterogeneity of normative deviations in brain structure [1].

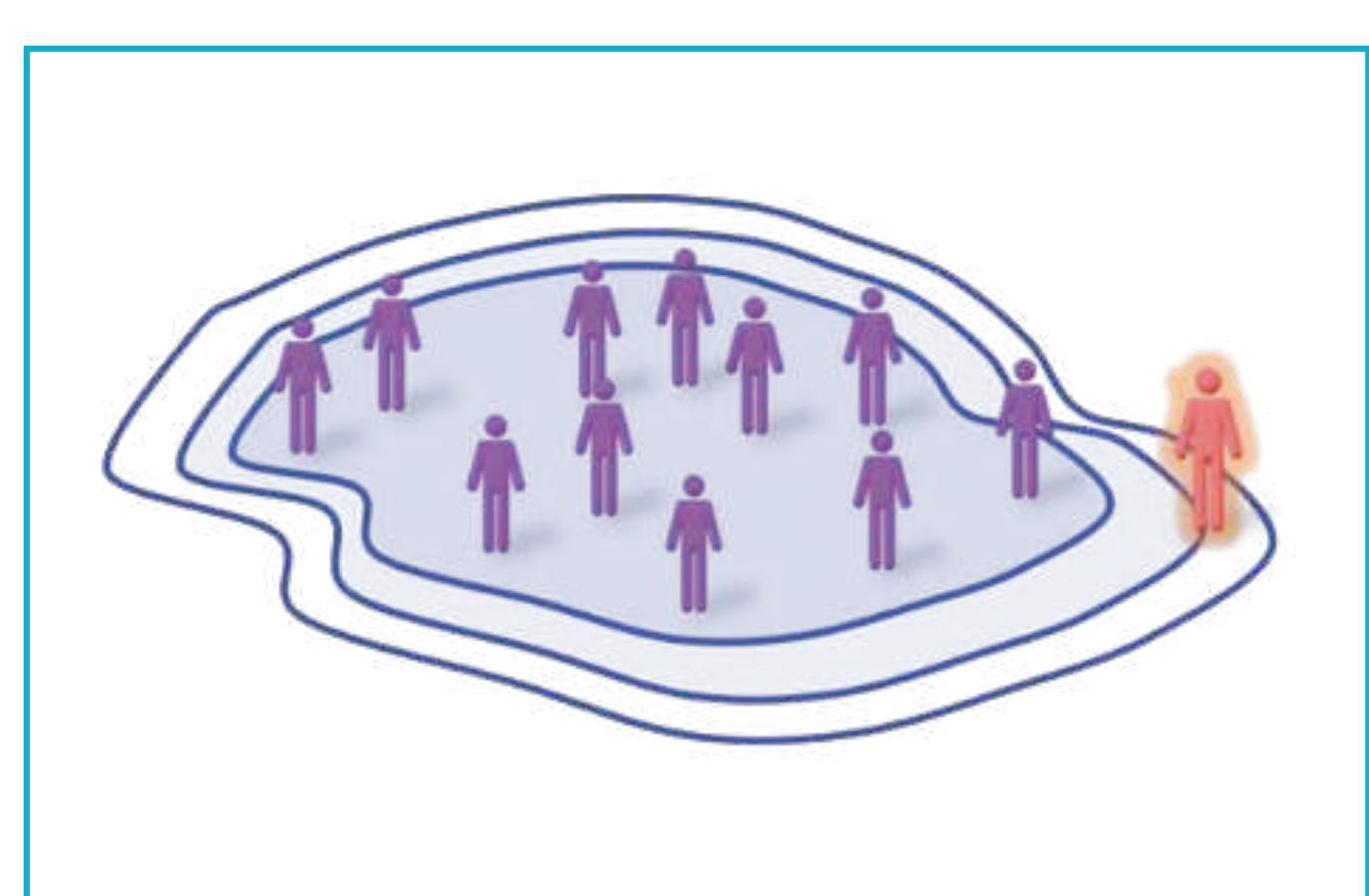


* WHO growth charts, CDC (2009)

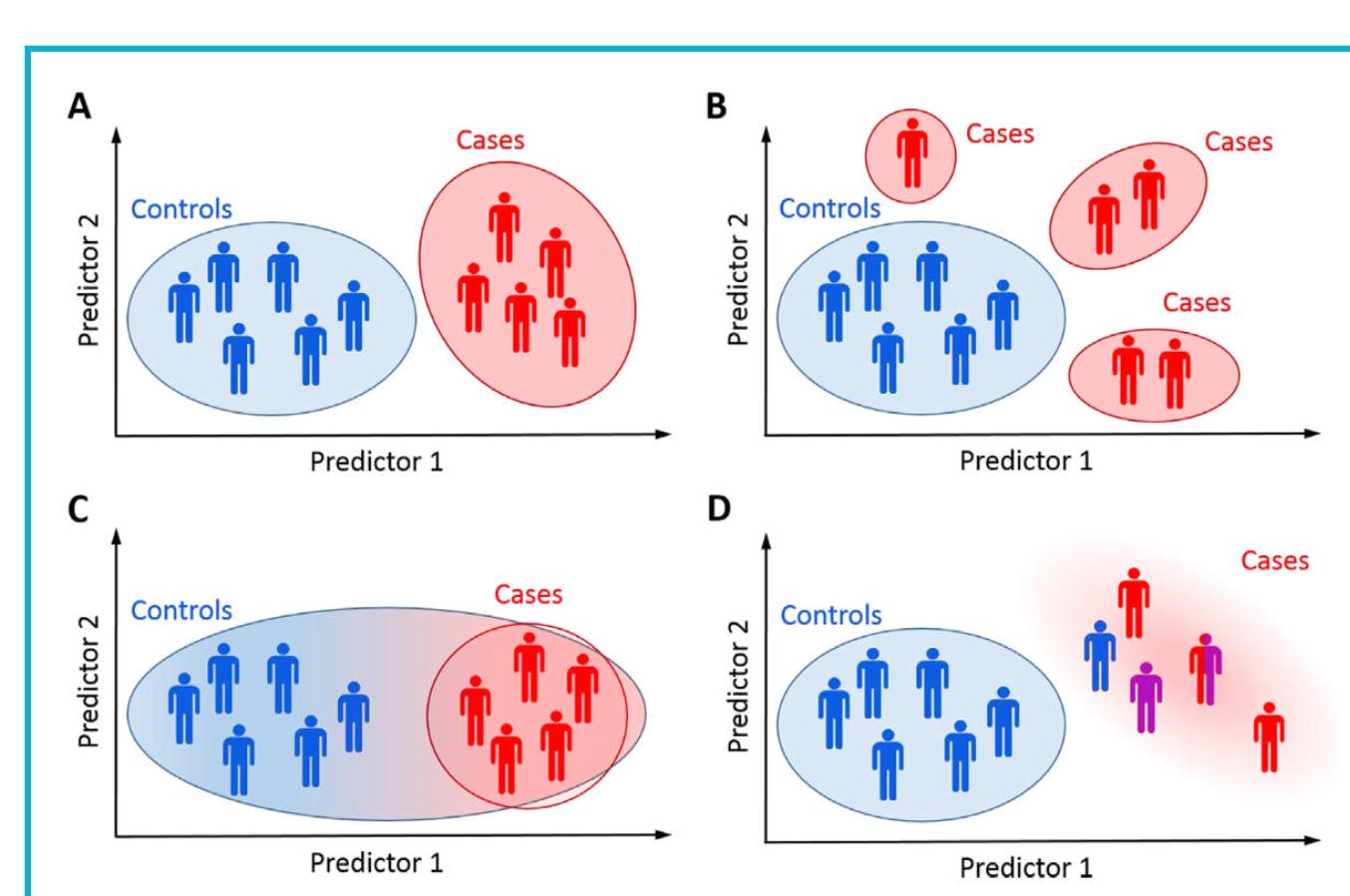


* [1] Marquand et al. (2019)

Notably, NMs help identify abnormalities as biomarkers for pathology at the level of individuals. Where pathology can be studied as individually-distinct deviations from the normal range [2].



* [1] Marquand et al. (2019)

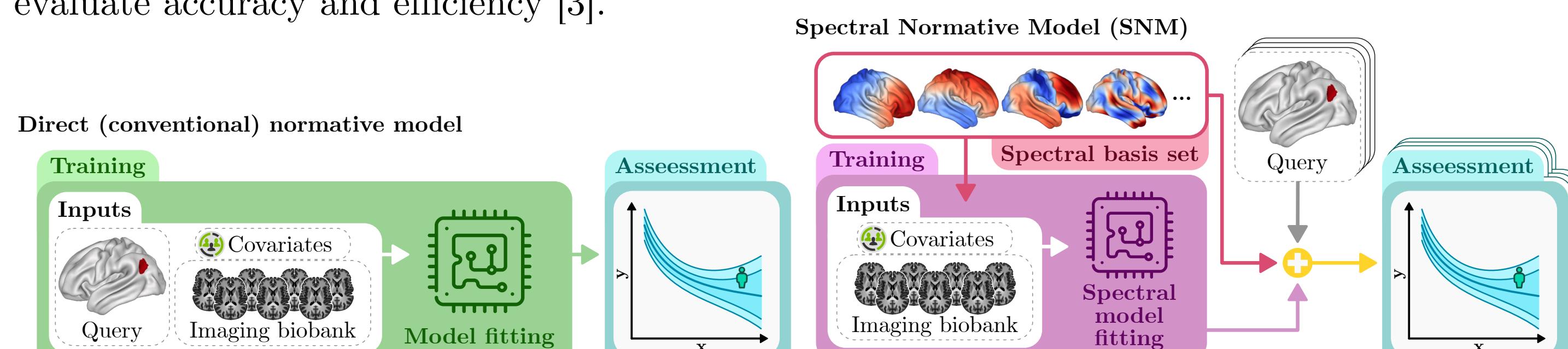


* [2] Marquand et al. (2016)

Normative modeling is limited by constraints in spatial resolution and flexibility. We propose the **Spectral Normative Modeling (SNM)** a framework for efficient, flexible normative inference across spatial scales, and demonstrate its application to Alzheimer's disease.

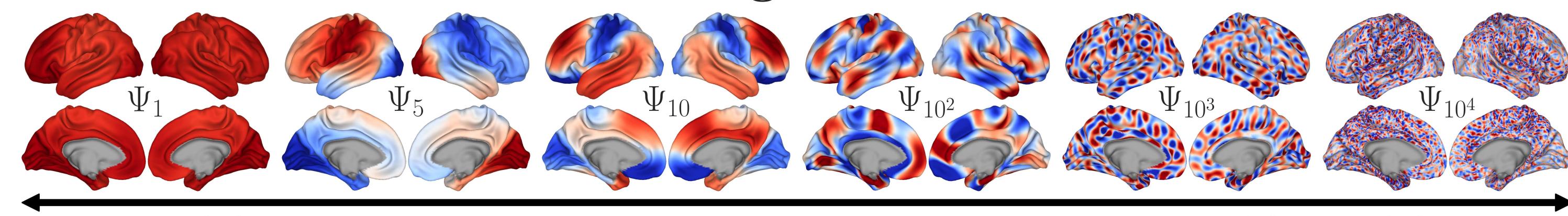
Methods

Model training utilized data from three **Human Connectome Project (HCP)** cohorts covering 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. SNM's performance was benchmarked against conventional NMs to evaluate accuracy and efficiency [3].



Computing **high-resolution NMs** is challenging due to the dimensionality of the feature space. A low-dimensional basis to encode cortical phenotypes can lay the foundations of computationally tractable high-resolution NMs. To this end, we utilized brain connectivity **eigenmodes** [4, 5] as basis functions for information reconstruction.

Brain eigenmodes

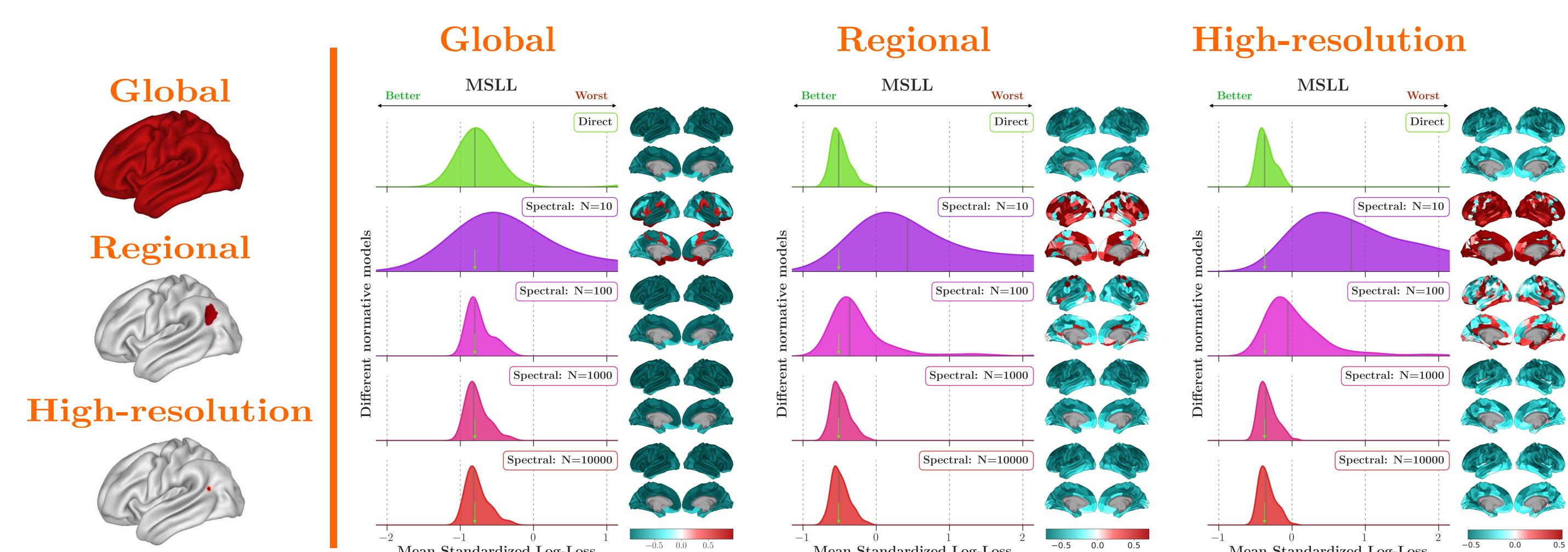


- Thickness loading on each eigenmode formed a distinct spectral thickness coefficient.
- Separate NMs were trained to independently model each spectral thickness coefficient (as a function of age and sex while accounting for scanner/site effects).
- Cross-dependency structure of spectral thickness coefficients was also modeled.
- Pre-trained SNMs can generalize to unseen spatial normative queries.
- Pre-trained SNMs have transfer learning capabilities and can be fine-tuned to independent clinical samples.

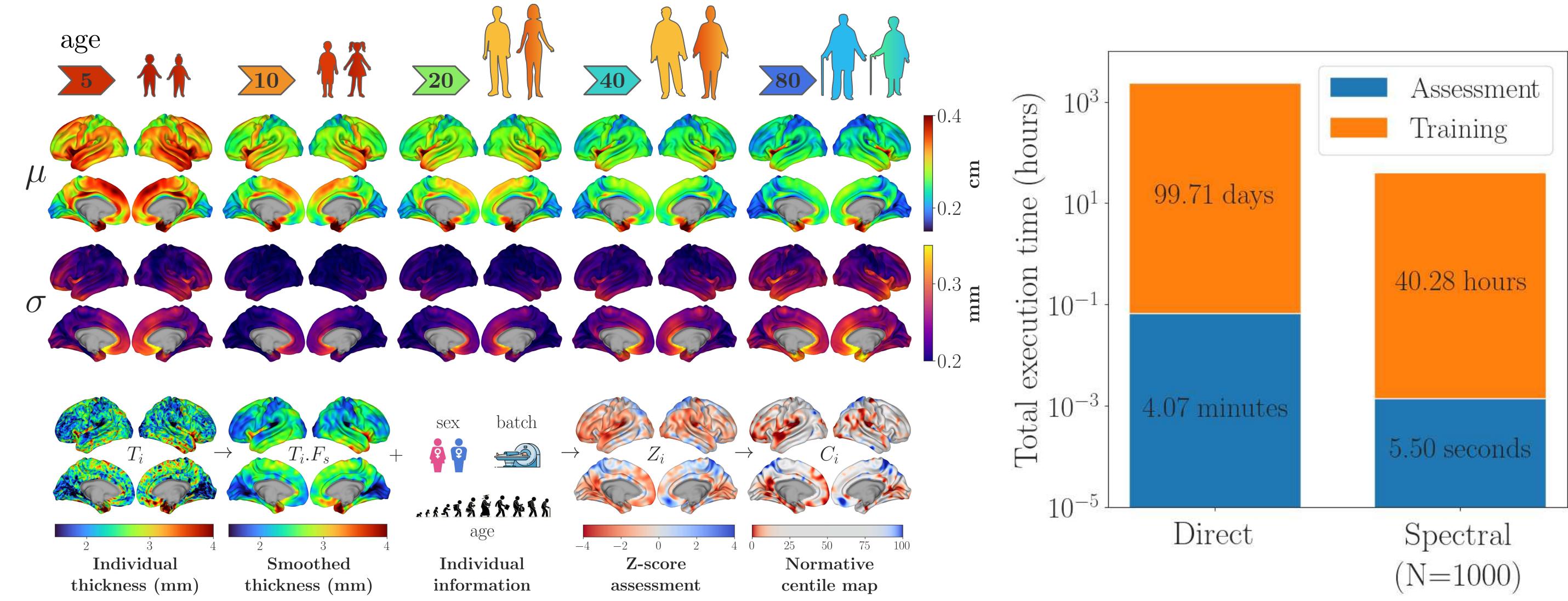
1. Marquand, A. F., et al. (2019). "Conceptualizing mental disorders as deviations from normative functioning". *Molecular psychiatry*, 24(10), 1415-1424.
 2. Marquand, A. F., et al. (2016). "Understanding heterogeneity in clinical cohorts using normative models: beyond case-control studies." *Biological psychiatry* 80.7, 552-561.
 3. Kia, Seyed Mostafa, et al. (2020). "Hierarchical bayesian regression for multi-site normative modeling of neuroimaging data." *MICCAI 2020, Proceedings*, 699-709.
 4. Robinson, P. A., et al. (2016). "Eigenmodes of brain activity: Neural field theory predictions and comparison with experiment". *NeuroImage*, 142, 79-98.
 5. Huang, W., et al. (2018). "A graph signal processing perspective on functional brain imaging". *Proceedings of the IEEE*, 106(5), 868-885.

Results

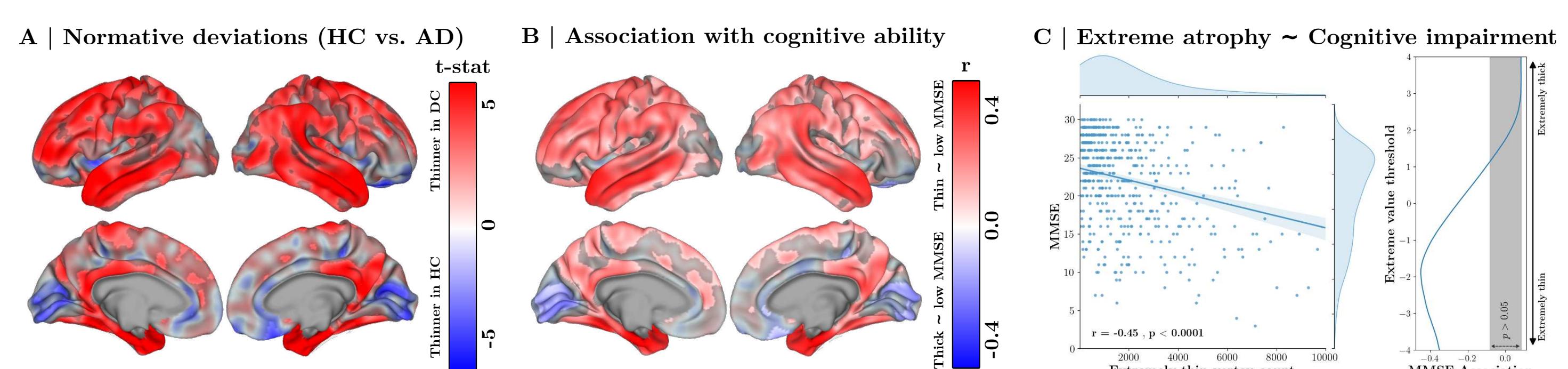
SNMs with as few as 1000 modes have a comparable performance to direct modeling:



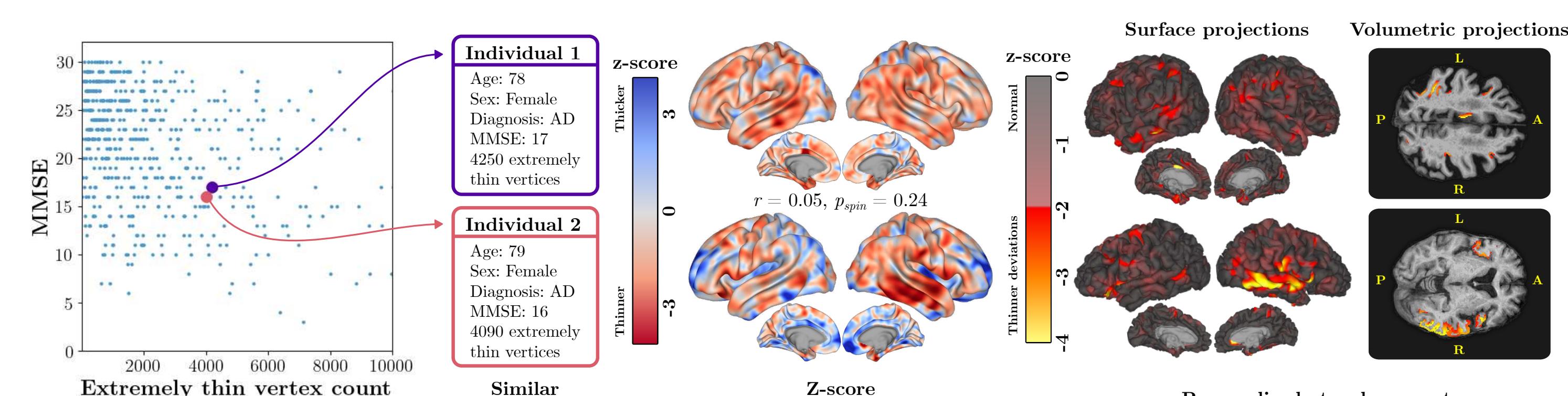
- SNM can achieve remarkable speedup while maintaining comparable performance.
- This enables efficient inference of lifespan normative ranges for arbitrary loci.



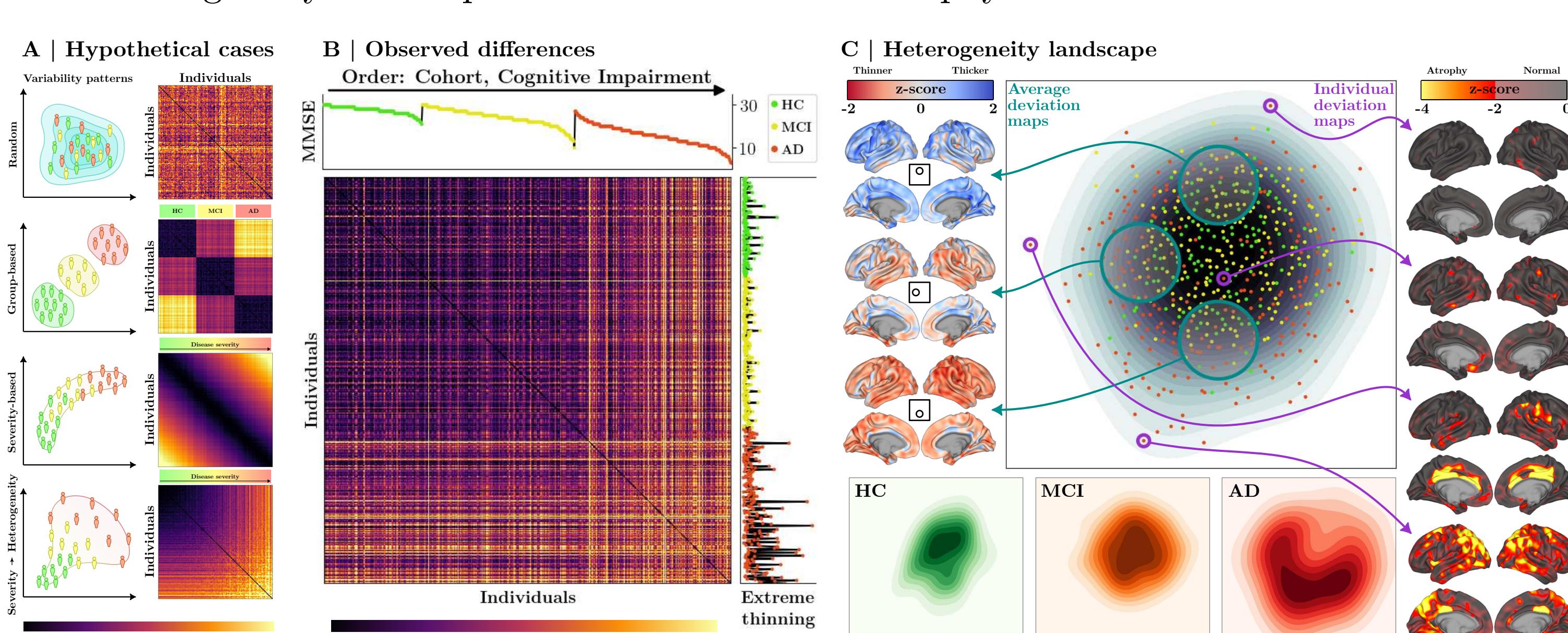
We illustrate SNM's translational utility by investigating cortical atrophy signatures associated with Alzheimer's disease (AD) dementia in a clinical cohort (N=674):



Individual atrophy maps can be widely different across dementia individuals:



Heterogeneity landscape of dementia-induced atrophy:



Concluding remarks

- We introduce a high-resolution approach to normative modeling, leveraging pretrained spectral normative models (SNMs) constructed from brain eigenmodes.
- SNM enables accurate, efficient estimation of normative ranges across spatial scales.
- Opens new avenues for precision brain charting across the human lifespan and biomarker development for clinical studies.
- The model reveals marked heterogeneity in AD-associated atrophy at the individual level, while enabling more personalized assessments.