mmNormVAE: Normative Modelling on Multimodal Neuroimaging Data using Product-of-Experts Variational Autoencoder

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Introduction

- **Two-step** approach:
  - ➢ Train a model on data of healthy participants.
  - ➢ Apply trained model on disease patients to estimate patient-level deviations.
- Intuitively similar to anomaly detection.
- **Deep learning models (e.g. variational autoencoders)**
  - ✓ Learns to reconstruct data of healthy subjects.
  - ✓ Model less precise in reconstructing data of AD patients.

$$\textit{observed deviation} = \underbrace{\frac{1}{\textit{number of regions}} \sum_{i=1}^{\textit{number of regions}} (x_i - \hat{x}_i)^2}_{\text{Mean squared reconstruction error}}$$

Challenges:

- Existing VAE normative models have unimodal structure.
- AD is **multifactorial**, showing deviations from the norm in features across multiple imaging modalities.
- Multiple modalities provide complementary information.

Contributions

- **Multimodal variational autoencoder (mmNormVAE)**
- Model joint distribution between multiple MRI modalities using **Product-of-Experts** (PoE) approach
- Use **mmNormVAE as a normative model** to estimate subject-level deviations of AD patients

Data

Healthy subjects (N = 9875) → **UK Biobank**

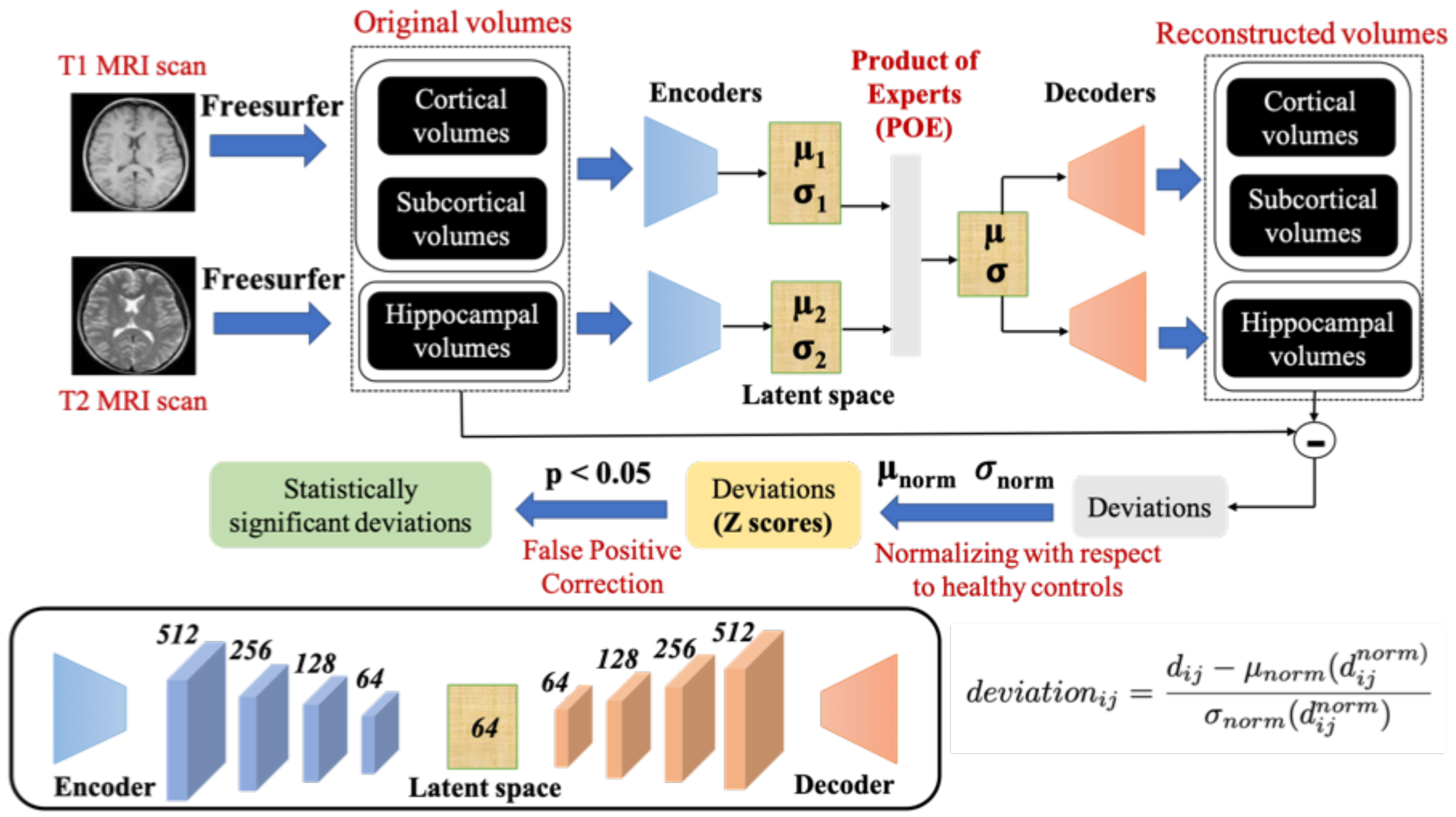
- ✓ Excluding all subjects with recent history of depression and other mental disorders.

Disease patients (N = 862) → **Alzheimer's Disease Neuroimaging Initiative (ADNI).**

Freesurfer to estimate brain volumes from **T1/T2 MRI** images.

- ✓ 64 cortical, 35 subcortical, 16 hippocampal.

Multimodal Normative Modelling



$$deviation_{ij} = \frac{d_{ij} - \mu_{norm}(d_{ij}^{norm})}{\sigma_{norm}(d_{ij}^{norm})}$$

$$\boxed{p(z|x_1,..,x_N)} = \frac{p(x_1,..,x_N|z) * p(z)}{p(x_1,..,x_N)} = \frac{p(z)}{p(x_1,..,x_N)} * \prod_{i=1}^{N} p(x_i|z)$$

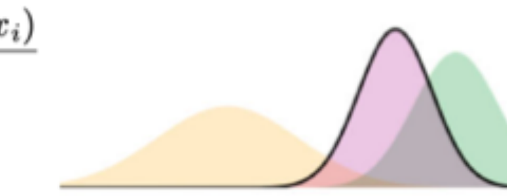
Assumption: Modalities are conditionally independent

$$= \frac{p(z)}{p(x_1,..x_N)} * \prod_{i=1}^{N} \frac{p(z|x_i)p(x_i)}{p(z)}$$

$$= \frac{\prod_{i=1}^{N} p(z|x_i)}{\prod_{i=1}^{N-1} p(z)} * \frac{\prod_{i=1}^{N} p(x_i)}{p(x_1,..x_N)}$$

$$\propto \frac{\prod_{i=1}^{N} p(z|x_i)}{\prod_{i=1}^{N-1} p(z)}$$

Joint posterior



Product-of-Experts (Wu and Goodman, 2018)

Prior expert

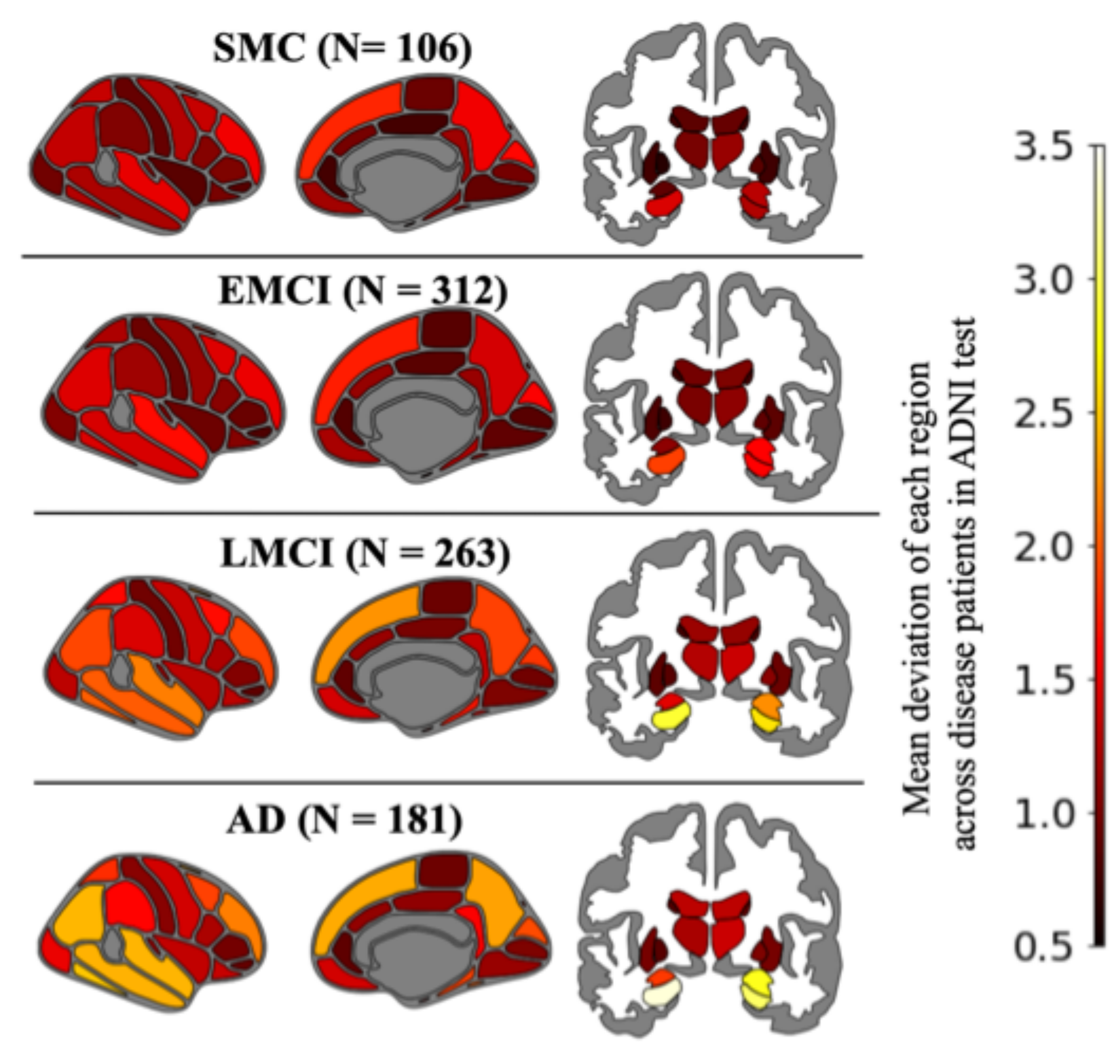
Modality-specific posterior

$$\boxed{p(z|x_1,..,x_N)} \propto \frac{\prod_{i=1}^{N} p(z|x_i)}{\prod_{i=1}^{N-1} p(z)} = \frac{\prod_{i=1}^{N} [\tilde{q}(z|x_1)p(z)]}{\prod_{i=1}^{N-1} p(z)} = \boxed{p(z)} \prod_{i=1}^{N-1} \boxed{\tilde{q}(z|x_i)}$$

Loss function

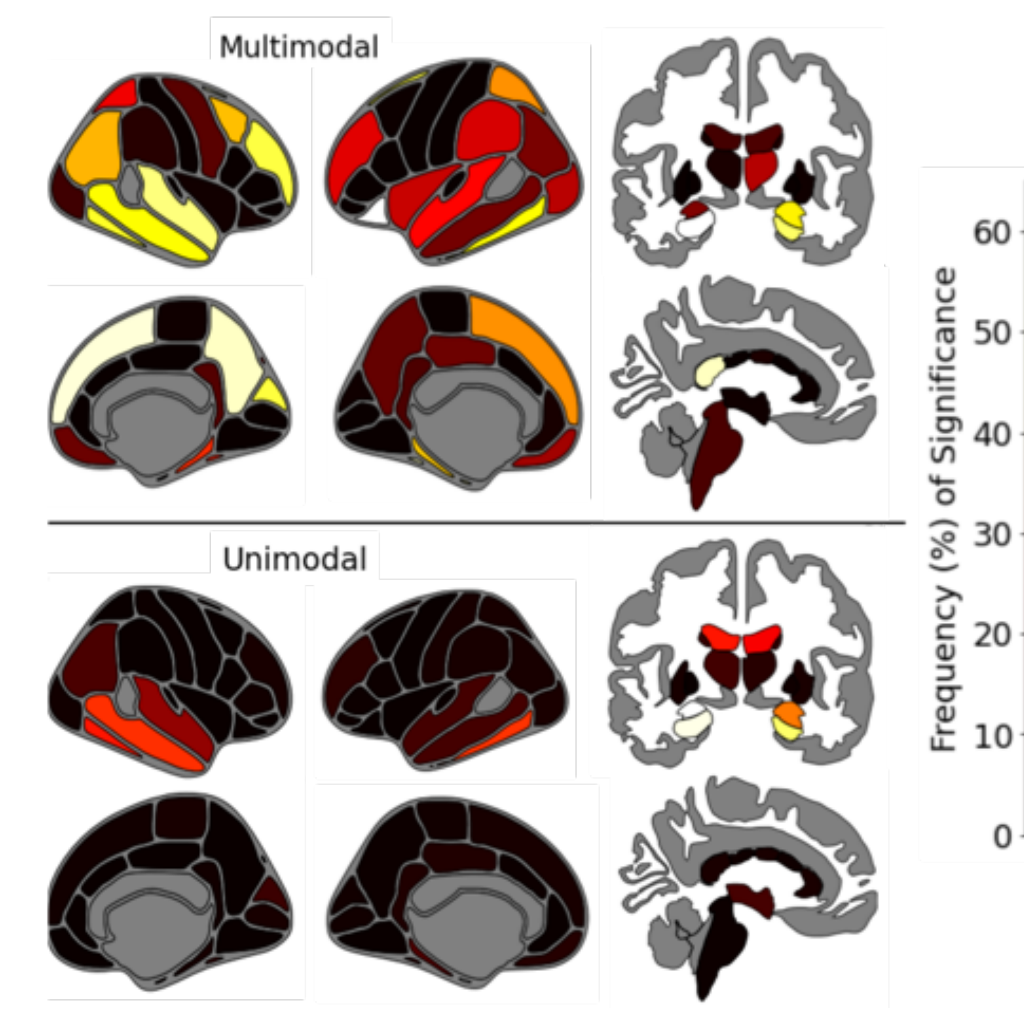
$$ELBO(X) = \underbrace{\mathbb{E}_{q(z|X)}\left[\sum_{x_i \in X} \lambda_i \log p_\theta(x_i \mid z)\right]}_{\text{Summation of reconstruction losses across modalities}} - \underbrace{\beta KL(q_\phi(z \mid X) \| p(z))}_{\text{KL divergence between joint-modality posterior and Gaussian prior}}$$

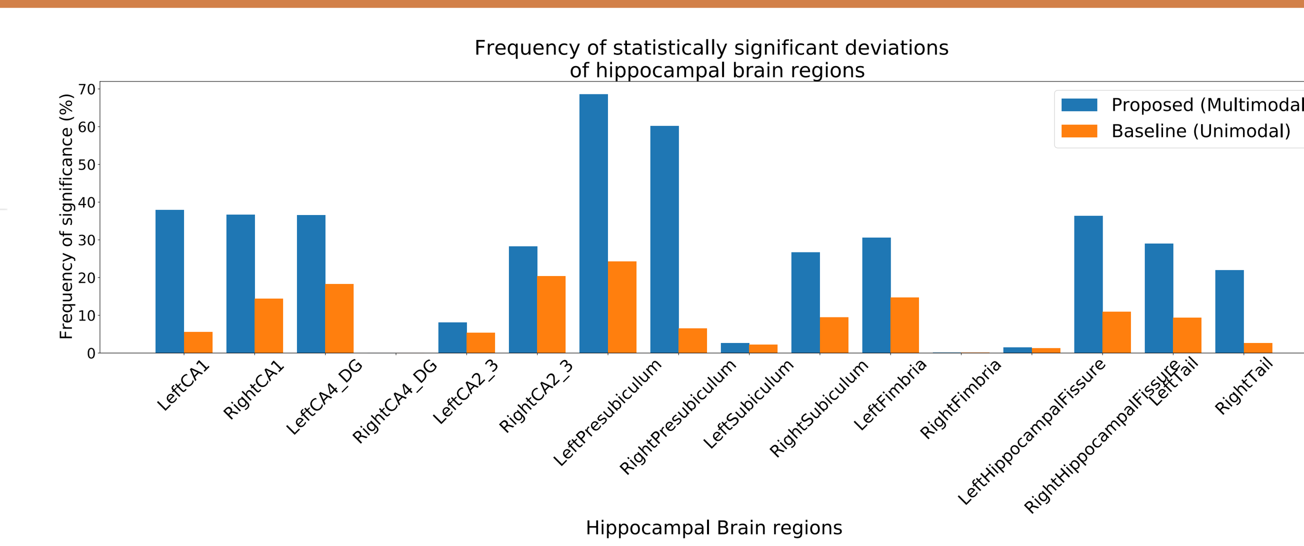
Experimental Results



Deviation maps: Mean deviations for each region (across all patients).

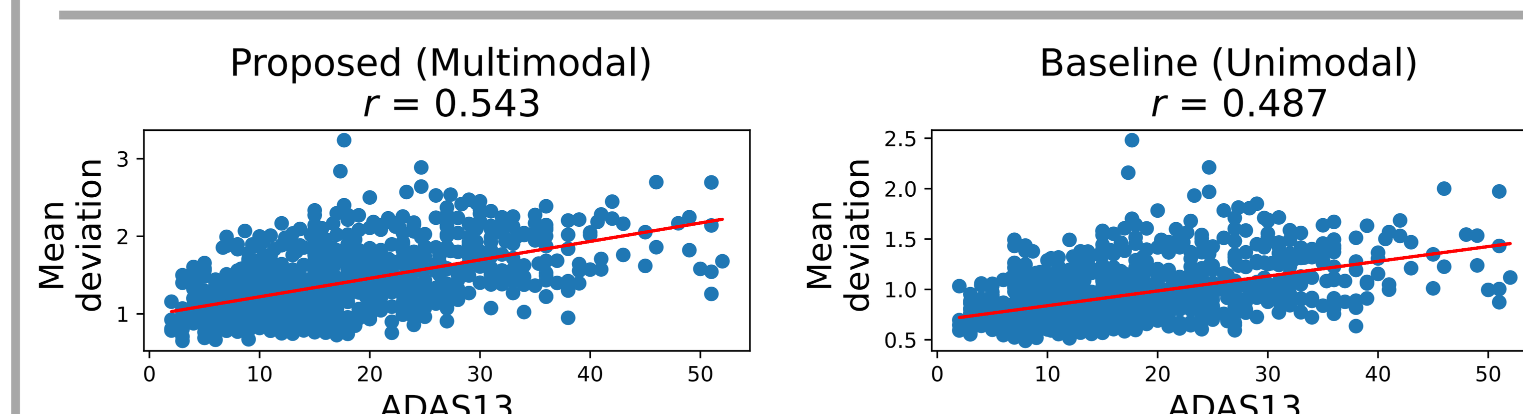
Region-wise deviations increase with the severity of the disease.





Frequency of Significance: Number of times each **cortical and subcortical region** (T1-weighted MRI) has **statistically significant deviations** from healthy subjects ($p < 0.05$)

mmNormVAE has more significant regions compared to unimodal baseline



- **ADAS13** → Level of **cognitive disfunction** in AD.
- **High scores** = **greater loss** in memory and cognition due to AD.

mmNormVAE deviations have higher correlation with cognition