Development of machine learning models for the detection of neurodegenerative diseases in neuroimaging data

Normative Modeling Using Autoencoders

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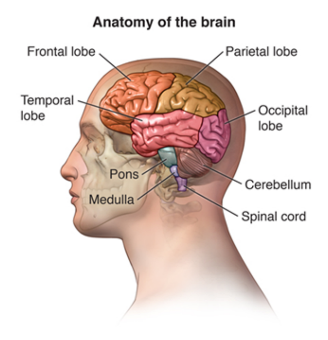
Introduction - Theoretical Background

Brain Anatomy

- Left and Right Hemisphere
- Frontal, Occipital, Parietal and Temporal lobe



[a]

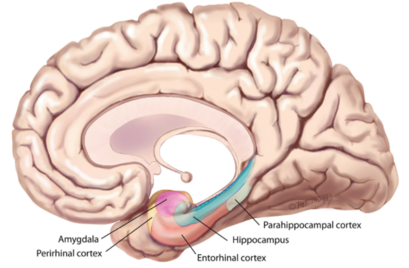
Brain Atrophy: a reduction in the volume of subregions of the brain that is often associated with cognitive decline.

[a] Magnetic Resonance Imaging (MRI) of the Spine and Brain, John Hopkins Medicine

Neurodegenerative Diseases

- Mild Cognitive Impairment (MCI): Characterized by a decline in cognitive abilities that exceeds the normal age-related changes, but not to the extent required to be diagnosed as dementia.
- Alzheimer's Disease (AD): The most common type of dementia. It is a progressive neurodegenerative disorder leading to memory loss and cognitive decline.

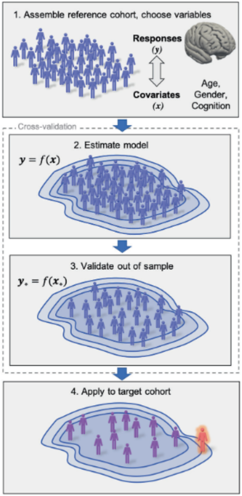
Both Alzheimer's disease and mild cognitive impairment affect the hippocampus and entorhinal cortex regions early in their course.



[b]

[b]Memory Part 2: The Role of the Medial Temporal Lobe, DOI: https://doi.org/10.3174/ajnr.A4169

Normative Modeling



[c]

A normative modeling technique is a computational approach used to establish and characterize the typical or "normative" patterns within a given dataset. Steps:

- Selection of the reference group and the variables.
- Estimation of the normative model.
- Out-of-sample validation.
- Application of the estimated model to a targeted clinical group.

[c]Conceptualizing mental disorders as deviations from normative functioning, DOI: 10.1038/s41380-019-0441-1

Normative Modeling

Advantages over traditional methods (group averages):

- More personalized approach: Instead of relying on group averages that may obscure individual variations, normative modeling focuses on each individual's unique deviations from established standards.
- Identifies subtle changes in brain structure and function long before clinical symptoms appear.
- Provides a holistic view of the factors that contribute to brain disease.

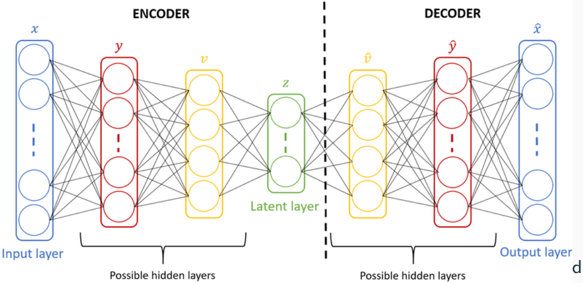
Vanilla Autoencoders

Structure and Hyperparameters:

- Encoder f_ϕ
- Decoder g_θ
- Latent space (layer) z

- Activation functions
- Number of hidden layers
- Number of neurons in each layer, particularly in latent space

Loss Function: $|f_\phi(g_\theta(x)) - x|$



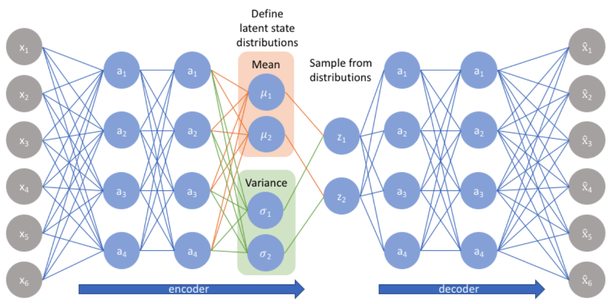
[d]

[d] https://www.researchgate.net/figure/General-architecture-of-a-deep-autoencoder_fig1_342529907

Variational Autoencoders

Vanilla Autoencoder drawback: lack of regularity of latent space, learns to produce a vector with size m < n, where n is the size of input

Variational Autoencoder: learns to produce 2 vectors with size m < n, which represent the parameters (mean value and standard deviation) of one distribution. From this distribution the latent vector is sampled.



[e]

[e] https://www.jeremyjordan.me/variational-autoencoders/

Variational Autoencoders

Regularity of latent space:
Loss function (Evidence Lower Bound - ELBO) consists of two components:

$$\log p_\theta(x) \geq \mathbb{E}_{q_\phi(z|x)}[\log p_\theta(x|z)] - \beta \cdot \mathrm{KL}(q_\phi(z|x) \| p_\theta(z)) \quad = \mathcal{L}(x; \theta, \phi)$$

- a reconstruction loss component, which forces the encoder to produce latent features that minimize the reconstruction loss (similar to an AE - Autoencoder)
- a KL (Kullback-Leibler) loss component, which forces the distribution generated by the encoder to be similar to the prior probability of the input vector, which is considered normal, thus pushing the latent space towards regularity.

Hyperparameter β adjusts the trade-off between the two components

Methodology

Datasets

- UK Biobank: 4517 subjects
- Alzheimer's Disease Neuroimaging Initiative (ADNI): 2398 subjects

Dataset / Features	Age	Sex	ICV	Diagnosis
UK Biobank	44-55	M-F	Intracranial Volume	CN
ADNI	54-91	M-F	Intracranial Volume	CN, MCI, AD

Table 1: Demographics of the datasets except volumes of ROIs

Experiment I: Simulated Atrophy Detection in semi-synthetic data

- Atrophy Simulation
- Adjustment for confounders (intracranial volume) with linear regression

- Standard Scaling
- Training Models in dataset without atrophy
- Testing Models in dataset with simulated atrophy

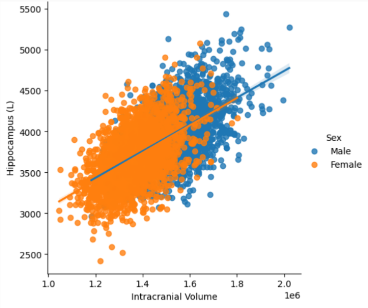


Figure 1: Before adjustment

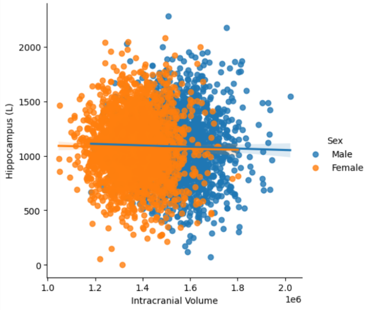


Figure 2: After adjustment

Experiment II: Atrophy Detection in real data and classification

- Adjustment for confounders (intracranial volume, age) with linear regression
- Standard Scaling

- Training Models in UK Biobank
- Testing Models in ADNI

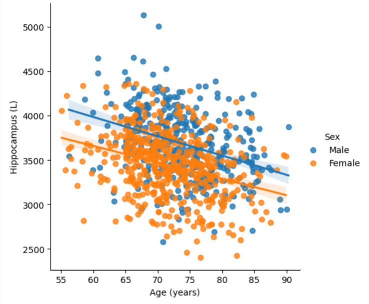


Figure 3: Before adjustment

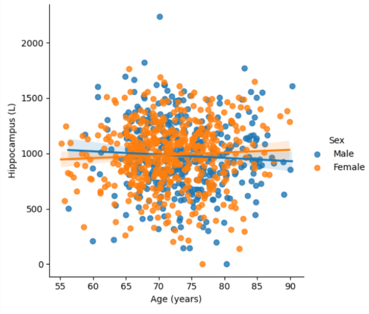


Figure 4: After adjustment

Experiment II: Classification with Normative Model vs. SVM

- Support Vector Machines (SVMs) work by finding the optimal hyperplane that maximizes the margin between different classes in a dataset.
- Reconstruction error $= y_{predicted} - y_{actual}$

Normative Model:

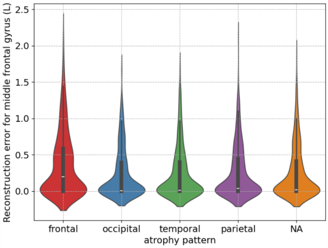
- Features and labels separation in ADNI
- Training model in UK Biobank
- Reconstruction error in ADNI calculation (using only features)
- Classification based on Reconstruction error

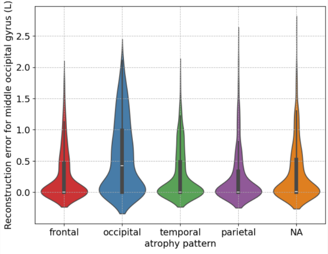
Support Vector Machine:

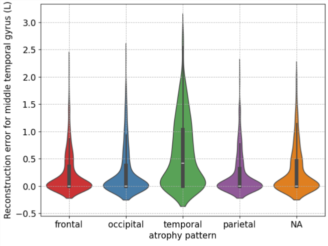
- Features and labels separation in ADNI
- Training SVM in ADNI (using labels)
- Classification with SVM

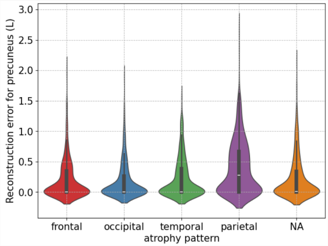
Results

Results: Experiment I, Vanilla Autoencoder







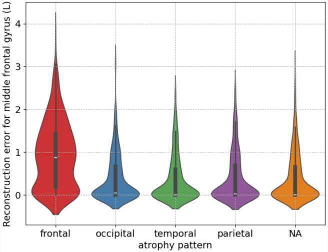


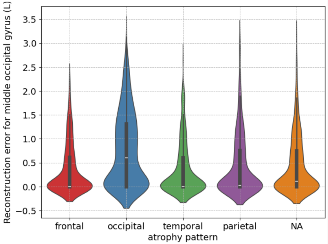
Results: Experiment I, Vanilla Autoencoder

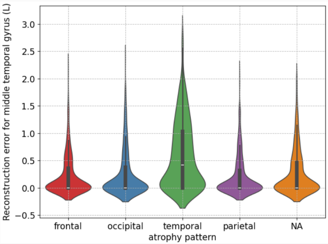
Atrophy pattern/Region	Frontal	Occipital	Temporal	Parietal
Frontal lobe	**0.3471**	0.2434	0.2420	0.2360
Occipital lobe	0.2555	**0.3596**	0.2535	0.2473
Temporal lobe	0.2500	0.2518	**0.4475**	0.2452
Parietal lobe	0.2599	0.2437	0.2811	**0.4053**
no atrophy	0.2651	0.2566	0.2785	0.2717

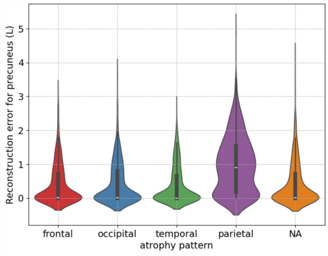
Table 2: Mean Reconstruction Error with Vanilla Autoencoder

Results: Experiment I, Variational Autoencoder







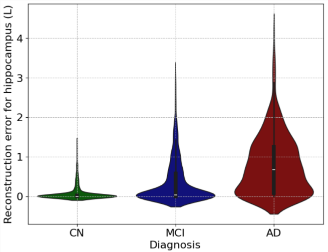


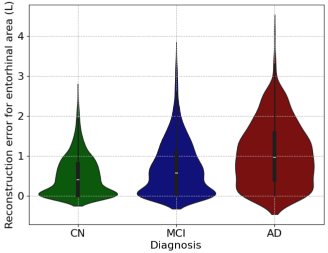
Results: Experiment I, Variational Autoencoder

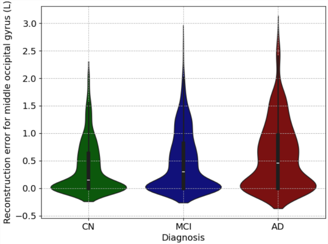
Atrophy pattern/Region	Frontal	Occipital	Temporal	Parietal
Frontal lobe	**0.7279**	0.4031	0.3983	0.3913
Occipital lobe	0.3938	**0.7126**	0.3942	0.3958
Temporal lobe	0.3834	0.3896	**0.7785**	0.3955
Parietal lobe	0.3927	0.4012	0.3972	**0.7518**
no atrophy	0.3870	0.3919	0.3937	0.3908

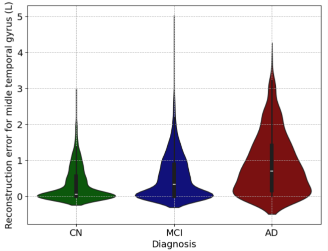
Table 3: Mean Reconstruction Error with Variational Autoencoder

Results: Experiment II, Vanilla Autoencoder

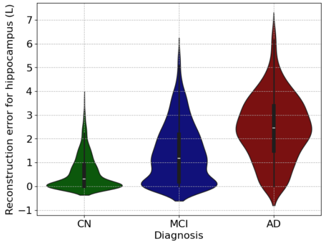


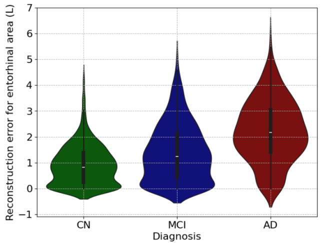


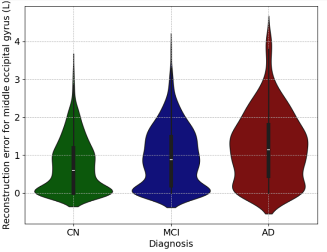


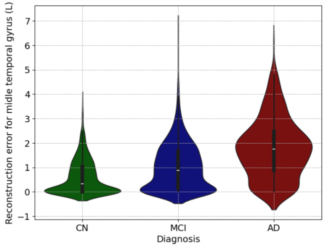


Results: Experiment II, Variational Autoencoder









Results: Experiment II, Classification

Classes / Model	AE	VAE	SVM
CN - MCI	0.6560	0.6797	0.6918
CN - AD	0.8321	0.8502	0.8910
MCI - AD	0.7191	0.7239	0.7450
CN - (MCI, AD)	0.7310	0.7146	0.7399
MCI - (CN, AD)	0.5451	0.5358	0.5449
AD - (CN, MCI)	0.7844	0.7803	0.8036

Table 4: Classification Results (AUC-ROC)

Conclusions

Conclusions

Normative Modeling:

- In the areas where atrophy has been simulated, the reconstruction error is higher. This is also confirmed by the data in tabular form.
- Slightly clearer differences are observed when comparing the reconstruction errors with the variational autoencoder compared with that of vanilla autoencoder (in both two experiments).

Conclusions

Classification:

- The variational autoencoder performs slightly better than the vanilla autoencoder most of the time, with minor differences in their results
- In binary classification, the results of normative models as classifiers are comparable to a traditional classifier (SVM)
- Classification with three classes using the "one versus rest" tactic provides satisfactory separation of healthy individuals (CN) and individuals with Alzheimer's disease (AD).

Discussion

Discussion

Advantages of proposal method:

- Label-Free Training
- Small number of labels required, only in preprocessing stage
- Application to Different Datasets and Diseases
- Supervision

Discussion: Future Steps

- Normative Modeling directly in MRI images, voxel based data (Convolutional Neural Network as a preprocessing stage)
- Exploration of latent space of Variational Autoencoder (dimensionality reduction)

Questions?