Parkinson's Disease Biomarkers: A Deep Learning Based Neuroimage Analysis

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting millions of people globally. There is no cure for PD, and current diagnostic methods are extremely subjective, relying only on observed motor and cognitive symptoms. Often, severe neuronal damage has occurred before any of these symptoms present. Identifying biomarkers for PD would aid greatly in early disease detection and improve prognosis for patients.

Past work from our group includes projects such as Parkinson's classification and feature extraction from diffusion tensor images and developing a graph convolution-based pipeline for exploring multimodal neuroimage data. This project furthers those efforts; our study aims to validate past biomarker studies by determining features that reliably distinguish PD patients from healthy control subjects in structural MRI data. This will be the first step in designing a predictive model of Parkinson's disease progression.

Data

T1-weighted anatomical MRI data from 111 subjects was downloaded from the Parkinson's Progression Markers Initiative (PPMI) database. PPMI is a longitudinal clinical study following around 400 untreated PD subjects and 200 healthy subjects for clinical, imaging and biospecimen biomarker assessment. Of the sMRI images we downloaded, 74 were from PD patients and 37 were healthy controls (HC).

The raw image data were preprocessed using fMRIPrep. The fMRIPrep software is a robust preprocessing pipeline for multiple neuroimage modalities including sMRI, fMRI, and dMRI.
On each image, we performed:

- intensity non-uniformity correction
- skull stripping
- spatial normalization (registration to the MNI brain atlas)
- voxel-wise brain tissue segmentation

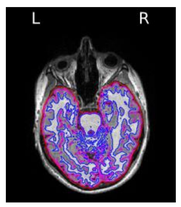

Figure 1. Brain extraction mask

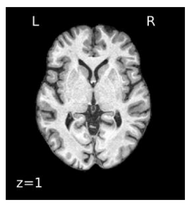

Figure 2. Post skull stripping

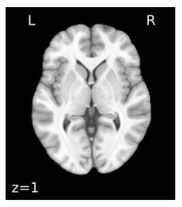

Figure 3. Post MNI normalization

Methods

Deep learning networks excel when it comes to classical computer vision tasks, such as classification or clustering on image data. However, most traditional neural network architectures do not perform as well on 3-dimensional data, such as the MRIs we wish to analyze.
With these considerations in mind, some of the specific details of our chosen model are outlined below:

- a hierarchical vector-quantized variational autoencoder (VQ-VAE) specifically adapted for 3-dimensional data
- VQ-VAE is a powerful generative model that learns discrete latent representations without supervision
- Preliminary results have shown that this generative model yields high reconstruction fidelity and best preserves the neuromorphology of the brain
- Hierarchical nature allows for learning of global (whole brain image) features independently of more local features (specific brain regions)
- The architecture for the VQ-VAE is pictured to the right, in figure 4.

Avenues for Analysis

Preliminary results demonstrate that our generative model can successfully reconstruct sMRI images. After training the model, the next step is to check if the learned latent distribution has found a structure in the data for PD vs HC patients. Training the model can be thought of as a dimensionality reduction method. The latent vectors learned by the model are transformed representations of the original data, representations that ideally only contain the most relevant data in the neuroimages. Therefore, we will use the embedding vectors as feature vectors. An approach to this clustering task is described below:

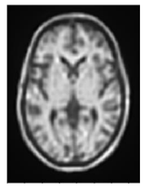

Figure 5. Reconstruction after VQ-VAE is halfway trained

- Spectral clustering is indirectly/implicitly imposing a graph structure on latent data.
- With a spectral clustering algorithm, we anticipate to find that the vectors separate out into two categories, healthy subjects vs. PD patients.
  - Since the data is detailed, may even see subtypes emerge based on severity
- What does this mean for finding biomarkers of PD in the brain?
  - Association between latent vector and original data is highly nonlinear
    - We may attempt to pull out direct association by perturbing the data and see how it affects data, and the other way around

An *activation atlas* is a way of visualizing the global view of a network. The feature visualizations of averaged activations can be explored in any model that uses convolutional layers, including VQ-VAE. An example activation atlas is pictured to the right. This may be a valuable tool for exploring the latent layers in our data, helping us understand how data is treated in the network and how this may affect the latent vectors.

Figure 6. Activation atlas [5].

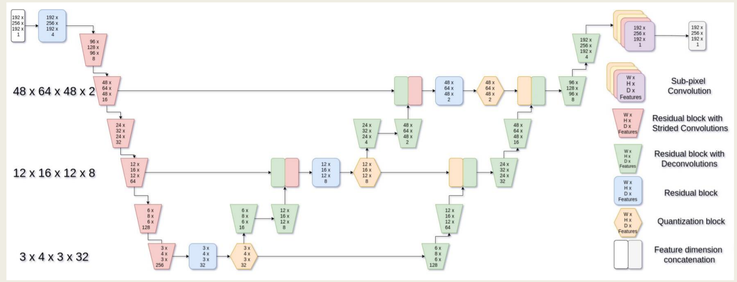

Figure 4. Architecture of the 3D VQ-VAE model we used on our data [1: Tudosiu et al. 2020].

Discussion

While VQ-VAE models are very powerful, they also require large training times, up to several days. Brain MRI data is also quite detailed, and its preprocessing requires several hours per image. As such, we were a bit limited by time and available hardware.

Issues may arise with clustering. Since our model is hierarchical, the latent vectors are all in different dimensions. Additionally, the discrete nature means that there is no guarantee that similar vectors are near each other and meaningful in the space. However, we anticipate that with spectral clustering we will be able to pull out a distinction between PD and HC subjects. Such an approach is promising and may even help with PD subtyping, if the clustering algorithm recognizes severity.

Future Directions

Though the specific project presented here is a work in progress, after its conclusion, there are several possible avenues for further exploration of this topic.

Our research only considered structural MRI images. Multiple neuroimage modalities best characterize brain areas on both structural and functional levels, which would allow various potential biomarkers to be examined. As such, we would like to extend our analysis to include functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) data, both of which the PPMI dataset provides.

Our ultimate goal is to build a pipeline to analyze PD subtypes and progression over time. This would contribute greatly towards bettering patient prognosis. However, modelling progression in the latent space is a very challenging problem. Our current model is simply a foundation for a latent spatio-temporal representation of PD and its progression.

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References

1. Tudosiu, P.D., Varsavsky, T., Shaw, R., Graham, M., Nachev, P., Ourselin, S., Sudre, C.H. and Cardoso, M.J.. "Neuromorphologicaly-preserving Volumetric data encoding using VQ-VAE" *ArXiv preprint,* 2020.
2. Sivakumar, Rajeswari, Shannon Quinn. "Parkinson's Classification and Feature Extraction from Diffusion Tensor Images" *Proc. Of the 18th Python in Science Conf.,* 2019.
3. McDaniel, Christian, Shannon Quinn. "Developing a Graph Convolution-Based Analysis Pipeline for Multi-Modal Neuroimage Data: An Application to Parkinson's Disease" *Proc. Of the 18th Python in Science Conf.,* 2019.
4. Bowman FD, Drake DF and Huddleston DE. "Multimodal Imaging Signatures of Parkinson's Disease." *Frontiers in Neuroscience,* 2016. 10:131. doi: 10.3389/fnins.2016.00131
5. Carter et al. "Exploring Neural Networks with Activation Atlases." 2019. https://distill.pub/2019/activation-atlas/

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Results included in this manuscript come from preprocessing performed using FMRIPREP version stable [1, 2, RRID:SCR_016216], a Nipype [3, 4, RRID:SCR_002502] based tool. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using N4BiasFieldCorrection v2.1.0 [5] and skull-stripped using antsBrainExtraction.sh v2.1.0 (using the OASIS template). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c [7, RRID:SCR_008796] was performed through nonlinear registration with the antsRegistration tool of ANTs v2.1.0 [8, RRID:SCR_004757], using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast [17] (FSL v5.0.9, RRID:SCR_002823).