BRAIN CONNECTIVITY MAPPING WITH STRUCTURAL MRI

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List of Notations & Abbreviations

MRI magnetic resonance imaging 3

dMRI diffusion magnetic resonance imaging 3

FA fractional anisotropy 3

MD mean diffusivity 3

RD radial diffusivity 3

ROI region of interest 3

FMRIB functional magnetic resonance imaging of the brain

FNIRT FMRIB's nonlinear image registration tool 3

Introduction

Basal ganglia is a part of the human brain which is group of subcortical nuclei responsible primarily for motor control, as well as other roles such as motor learning, executive functions and behaviors, and emotions. [1] Huntington's disease is a disorder that causes the progressive degeneration of the basal nuclei. [2]

Hospital de Bellvitge provided an excellent dataset of magnetic resonance imaging (MRI) and diffusion magnetic resonance imaging (dMRI) records of 32 control and 37 Huntington patient records of T1 and T1/T2 MRI images with isotropic voxels of 1 millimeter resolution and dMRI fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) images with isotropic voxels of 2 millimeter resolution. Furthermore this dataset also contains the mask for the basal ganglia, which will also be referenced as the region of interest (ROI). Masks for the 7 main cortical regions of the brain, which will also be referenced as the target regions: Limbic, Executive, Rostral-Motor, Caudal-Motor, Parietal, Occipital and Temporal are also included in the dataset. Tractography was performed on the dMRI images to figure out which parts of the ROI are connected to which cortical target, in a similar manner to how it was done in this paper [3]; where the relative connectivity maps are representing the ratio of the number of streamlines to each cortical target. Furthermore, the raw streamline images are also available, where there are a maximum of 5000 streamlines from each voxel in the ROI. The subcortical segmentation of the Basal Ganglia is also available, for the Caudate, Putamen and Accumbens on the control records. And lastly FMRIB's nonlinear image registration tool (FNIRT) warp fields were also provided for converting the records into normalized space.

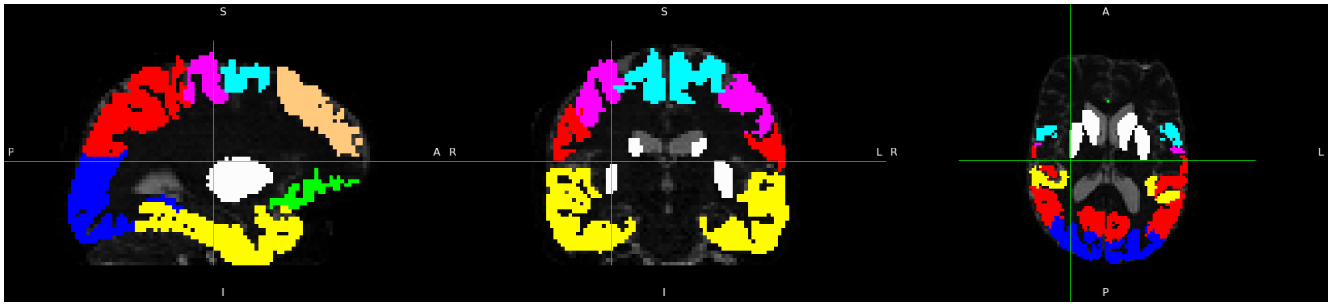

Figure 1.1: Basal Ganglia (ROI) & Cortical Targets

Color	Region
White	Basal Ganglia (ROI)
Green	Limbic
Brown	Executive
Light Blue	Rostral-Motor
Purple	Caudal-Motor
Red	Parietal
Blue	Occipital
Yellow	Temporal

Table 1.1: Regions Legend

Furthermore, for both the ROI and cortical targets, the dataset distinguishes between the right and left halves of the brain. Thus there are actually 2 ROIs and $2 \cdot 7 = 14$ target regions.

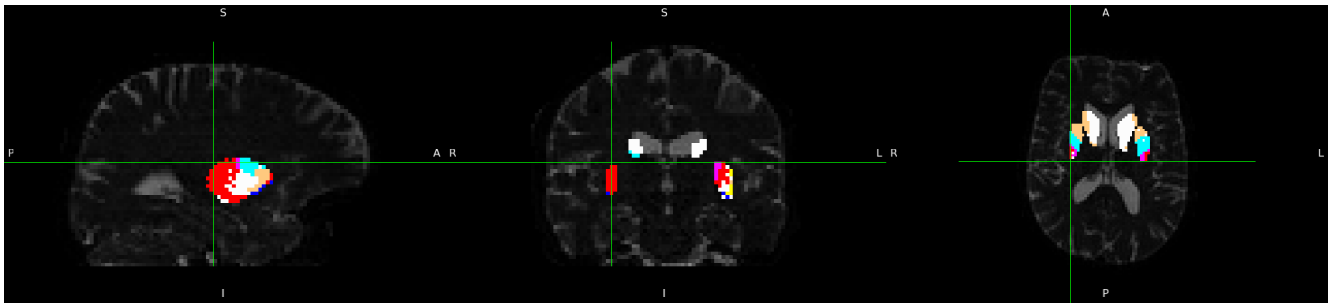

Figure 1.2: Connectivity Maps

Fulfillment of the Objectives

2.1 Objectives

The end goal is to predict the relative connectivity of the Basal Ganglia to the cortical targets, from the radiomics features of the T1 and T1/T2 images.

This being a very complex problem, there is the possibility that the correlation between the connectivity of the brain and the T1, T1/T2 images are too weak to be mapped on this dataset. As from a datascience perspective, 69 datapoints are not much. But from a medical perspective it is substantial as it is very hard to collect uniform, clean data, with permissions to use it for research.

A simpler task leading up to the complex end goal, is a model for the simple segmentation of the Basal Ganglia for the subcortical regions Caudate, Putamen and Accumbens. In order to confirm that the radiomics texture of the T1 and T1/T2 images of this dataset are are correlated to the segmentation of the Basal Ganglia. This problem is inherently connected to the main goal, as the relative connectivity does obey certain anatomical restrictions, and the subcortical segmentation of the Basal Ganglia is confirmed to be related to the relative connectivity. Thus if this simpler prediction fails, there is a good chance that the complex end goal will fail as well.

Another intermediate task, is a model for predicting FA and MD images. This is also related to the main goal, as these images are computed from the dMRI images, the same image that the relative connectivity was computed from. But it is inherently simpler, not needing to perform complex algorithms like tractography.

The biggest obstacle of this project is the preprocessing of the data, as there are many variations and hyperparameters that can be tuned. An exhaustive search definitely will not be viable, thus the preprocessing and model will needed to be tuned in a waterfall like manner, making educated guesses and comparing model performances across different tries. The main metric to measure model performance, will be the accuracy of the label prediction across voxels, as it should be comparable between all approaches. The accuracy metric will be used for the subcortical label prediction problem as well, and pearson correlation will be used as the metric to evaluate the FA and MD predictions.

2.2 Motivation

The motivation for predicting the connectivity maps from the T1 and T1/T2 MRI images, is skipping the time and resource consuming process performing dMRI and tractorgraphy.

2.3 Experiments

The following contributing factors are needed to be explored and experimented with:

- Experiment Type:
  - Basal Ganglia subcortical segmentation (classification)
  - Brain / Basal Ganglia diffusion FA and MD prediction (regression)
  - Basal Ganglia relative connectivity segmentation (classification)
  - Basal Ganglia number of streamlines prediction (regression)
- Input Space:
  - Native
  - Normalized
- Input Data:
  - T1
  - T1/T2
  - Mixed (T1 and T1/T2)
- Radiomics Extraction Parameters:
  - Kernel size
  - Bin width
  - Relative bin width (fixed number of bins)
- Additional Non-Voxel Based Radiomics Inputs:
  - Basal Ganglia
  - Entire Brain
  - Target Regions
- Left and Right Hemispheres:
  - Left only
  - Right only
  - Left and Right with concatenated label information (e.g. no differentiation between left and right target regions)
  - Left and Right with NOT concatenated label information (e.g. differentiation between left and right target regions)
- Control and Patient Datapoints:
  - Control only
  - Patient only
  - Mixed (Control and Patient)
- Additional Clinical Data Input
- Sequential Backward Feature Selection

- Feature Scaling and/or Normalization
- Relative Connectivity Thresholding
- Model Properties
  - General Architecture
    - Single FNN Model
    - Dual FNN Model (more on this later)
    - Mixture of Experts FNN Model (more on this later)
  - Model Size
    - Number of Layers
    - Layer Width
  - Activation Function
  - Batch Size
  - Early Stopping
  - Loss Function
  - Learning Rate
  - Regularization

As mentioned, an exhaustive search of the hyperparameter space is not feasible, thus it must be explored in a linear way. The following experiments are already done, or partially done:

- Basal Ganglia subcortical segmentation
  - Sanity Check: tried to predict it from T1 to make sure there is no direct correlation
  - Additional Non-Voxel Based Radiomics Inputs: experimented with additional non-voxel based radiomics features
  - Radiomics Kernel Sizes: experimented with including voxel based features with different kernel sizes
  - Short Conclusion: including multiple different kernel sizes are the best, non-voxel based features made no improvement, final test accuracy 0.91
- Brain / Basal Ganglia diffusion FA and MD prediction
  - FA: predicted FA in Basal Ganglia from many different kernel sizes (did not use any other features besides voxel based radiomics), yielded test pearson correlation of 0.92
  - MD: predicted MD in Basal Ganglia from many different kernel sizes (did not use any other features besides voxel based radiomics), yielded test pearson correlation of 0.83

After completing the two simpler exercises, and confirming the viability of the thesis, I moved onto the relative connectivity prediction. I ran experiments for the following 6 configurations:

- T1 native space
- T1/T2 native space

- T1 native space (excluding datapoints that are missing T1/T2 for fair comparison)
- T1 normalized space
- T1/T2 normalized space
- T1 normalized space (excluding datapoints that are missing T1/T2 for fair comparison)

Experiments:

- Single kernel size voxel based features
  - Additional non-voxel based features of target regions (single bin)
  - Additional non-voxel based features of basal ganglia (single bin)
  - Additional non-voxel based features of basal ganglia & whole brain (single bin)
- 4 different kernel sized voxel based features & 4 different bin sized basal ganglia features
- 2 different kernel sized voxel based features & 2 different bin sized basal ganglia features
- 5 different kernel sized voxel based features & single bin size basal ganglia features
- 4 different kernel sized voxel based features
- 9 different kernel sized voxel based features
  - control datapoints
    - left hemisphere
    - right hemisphere
    - both hemisphere
  - huntington datapoints
    - left hemisphere
    - right hemisphere
    - both hemisphere
      - included CAP clinical data
      - included CAP & UHRDs clinical data
      - included all clinical data
  - both control & huntington datapoints
    - left hemisphere
    - right hemisphere
    - both hemisphere

Tried two different model configurations, a simple FNN for classifying datapoints. And a dual model FNN, where one of them predicts the connectivity label and the other one is a regression model responsible for predicting the connectivity value of the strongest connection. The latter one can be used to 'reinforce' the not connected voxels, achieving a better accuracy. The best performing configuration so far was Native T1/T2, with all 9 voxel based features (without non-voxel based features), on control datapoints, with both left and right hemispheres included, yielding 0.62 accuarcy on the test datapoints. Some preliminary observations are:

- Right hemisphere datapoints are consistently easier to predict that left datapoints
- Control datapoints are consistently easier to predict that huntington datapoints
- Combining control and huntington datapoints inconsistently yielded same, or marginally better accuracy
- Combining right and left hemisphere datapoints inconsistently yielded same, or marginally better accuracy
- Including clinical data for the huntington datapoints resulted in less overfitting and better accuracy (BUT still worse than control datapoints)
- Multiple, larger kernel sizes are better (still experimenting what is the best)
- T1/T2 is better
- Including target region features resulted in less overfitting, and marginally worse accuracy
- Including basal ganglia features resulted in more overfitting, and worse accuracy
- Including basal ganglia and brain features resulted in more overfitting, and worse accuracy
- Dual FNN model (for not connected reinforcement) consistently yielded much better accuracy

Adjustments Made

The main adjustment was changing the focus of the main goal of predicting relative connectivity, to predicting FA and MD. Due to the yielded results being underwhelming, regardless that with further fine tuning we could get the accuracy up to maybe around 0.7 which is much-much better than random guessing. And the FA and MD predictions look more promising and easier to work with, so we want to focus the remaining resources on fine tuning and experimenting with those models.

Other deviations from the original plans, is that we are not even going to try using a highly explainable model (such as decision trees), as it is evident at this point that the complexity of this problem is beyond the capabilities of said models. Furthermore we will not try fully convolutional approaches, after realizing that it does not fit the original hypothesis of 'can we predict relative connectivity from the radiomic features'. As well as other technical limitations, as a simple U-net with 3 downasmple and 3 upsample layers, were already huge enough so it would only work with a maximum batch size of 1, on a GPU with 24GBs of VRAM.

And lastly we would like to change the title of the thesis to 'Brain Connectivity Mapping with Structural MRI' (waiting for a final confirmation from Estela) from 'Characterizing Neurodegeneration Patterns Using Radiomics' as it did not completely fit for what we are trying to do.

Work Plan for Completion

The remaining time and resources will be focused on completing the following tasks:

- Refine Train/Validation/Test splitting, as of right now it is not ensured that the splits contain the same ratio of asymptomatic and symptomatic huntington patients (it has been pointed out to me that asymptomatic patients' neurodegeneration is very similar to controls' meaning it can skew the results).
- Refine normalized space evaluation, as of right not it is not a completely fair comparison between native and normalized space. A solution will be implemented to 'de-normalize' the yielded predictions into native space, and compute the final metric in the native space, resulting in a more fair comparison.
- More detailed and in-depth experimentation for FA and MD predictions (similar to the relative connectivity experimentations).
- Finishing exhaustive feature selection on the relative connectivity (it is computationally expensive and it is half way done, and hopefully it can be used for FA and MD as well).
- One unorthodox idea that is yet to be tried is to append the coordinates of each voxel to the normalized input space. As the model could learn anatomical markers based on this.
  - An extension of this idea is to include the coordinates in native space as well. This by default would not make sense as the coordinates of voxels between different patients are not comparable in native space. But first extracting the coordinates in normalized space and then warping them back to native space by 'de-normalizing' them, could work.
- Fine tuning the best model for predicting voxels separately for each spaital location. This approach capitalizes on the same idea as including the voxel coordinates, as the fine tuned models could learn extra anatomical markers based on their spatial locations. (similarly, this only makes sense in normalized space)

Sources of Information

[1] José L Lanciego, Natasha Luquin, and José Obeso. "Functional neuroanatomy of the basal ganglia". In: *Cold Spring Harbor perspectives in medicine* (2012). URL: https://doi.org/10.1101/cshperspect.a009621.

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[3] Hyungyou Park et al. "Aberrant cortico-striatal white matter connectivity and associated subregional microstructure of the striatum in obsessive-compulsive disorder". In: *Molecular Psychiatry* (2022). URL: https://doi.org/10.1038/s41380-022-01588-6.