**Assessing microstructural brain differences in epileptic patients with vagus nerve stimulation via diffusion MRI, tractography and machine learning**

Summary

**Objective**

Epilepsy is a significant neurological disorder that affects millions of people world-wide [1]. Up to a third of epileptic patients have drug-resistant epilepsy [2]. In recent years, Vagus Nerve Stimulation (VNS) has emerged as a promising therapeutic intervention for drug-resistant epilepsy. Despite its clinical effectiveness, the underlying mechanisms of VNS are poorly understood, particularly concerning variability in treatment response [3].

Several studies have been conducted to predict the response to VNS. Mithani et al. [4] employed connectome profiling to identify responders to VNS, using machine learning algorithms to analyse diffusion data. This approach allowed them to find more connectivity and robust microstructures in the left-lateralized limbic system, thalamocortical connections and association fibres. Ibrahim et al. [5] highlighted the importance of presurgical thalamocortical connectivity in predicting response to VNS. They used machine learning algorithms to classify responders (R) and non-responders (NR) based on functional MRI data (fMRI). Enhanced connectivity in thalamocortical connections, anterior cingulate cortex and insular cortex were found.

Leveraging advanced diffusion magnetic resonance imaging (dMRI) techniques, including Diffusion Tensor Imaging (DTI), NODDI [6], DIAMOND [7] and Microstructure Fingerprinting [8], we quantitatively assess various microstructural metrics within specific Regions of Interest (ROI). These advanced models enable the computation of various metrics representing distinct biological aspects of microstructure.

By employing these techniques, we aim to identify specific biomarkers associated with R and NR. We extend the method by incorporating machine learning algorithms to predict R to VNS based on the relations of microstructural metrics.

**Methods introduction**

Data were collected from 19 patients with drug-resistant epilepsy. Diffusion weighted MRI images were pre-processed and corrected using the ElikoPy pipeline [9].

Microstructural models were estimated. DTI maps were obtained with the DiPy Library. The NODDI model was applied to the data using the DMIPY library. DIAMOND maps were computed using Benoit Scherrer's model [7]. The Microstructure Fingerprinting model was performed using the Python code provided by Rensonnet G [8]. We have extracted Fractional Anisotropy (FA), Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) from DTI, thresholded intracellular volume fraction (icvf), Orientation Dispersion Index (ODI), volume fraction of fibre bundles (fbundle), extracellular volume fraction (fextra) and intracellular volume fraction (fintra) from NODDI, weighted FA (wFA), wAD, wRD, wMD and total fraction of fibres (frac_ctot) from DIAMOND and fibre volume fraction (fvf_tot), weighted fvf_tot (wfvf) and total fraction of fibres (frac_ftot) from MF.

Three types of study have been done:

- Study with biological interpretation: we study the distribution of the metrics in a targeted volume region of the brain. To characterise a distribution, we compute the weighted mean, weighted standard deviation, weighted skewness, and weighted kurtosis, which are defined as the first four moments.

- Study without biological interpretation with Radiomics: we extract the features defined by the radiomics approach. Radiomics is a practice where medical images are converted into mineable data, explaining different properties of the selected tissue, such as shape and heterogeneity, and they are used to predict outcomes [10]. Radiomics is ROI based and it can extract hundreds of features from one single region, including statistical, texture and shape features.
- Deep learning classification: we use the computed 3D metrics map to train a deep learning model capable of classifying R and NR, without using ROI and feature extraction.

**ROI extraction**

For ROI extraction, we use FreeSurfer package, which is an open-source neuroimaging toolkit with many functions including labelling regions of the brain and registration.
The ROIs computed from FreeSurfer are into the anatomical space of T1 images, therefore they need to be registered into the dMRI space. To reach our result, we use ANTs software, which is considered a state-of-the-art medical image registration toolkit.

To generate regions of brain fibre fascicles we used TRACULA implemented in FreeSurfer and the library MRtrix3 which gives many tools for the processing of diffusion-weighted images. TRACULA (TRActs Constrained by UnderLying Anatomy) is a tool from FreeSurfer, for automatic reconstruction of the major tract based on Diffusion Weighted MRI data. TRACULA needs the cortical and subcortical parcellation from T1 data, and it uses the relative positions of anatomical structures with respect to each other to reconstruct the tractography of the main pathways. TRACULA gives the tractography of 42 pathways connections including the fornix, the cingulum, the longitudinal fasciculus, and the anterior thalamic radiation. But it does not give the rest of the thalamic radiations: posterior thalamic radiation, superior thalamic radiation, and thalamo-insular tracts. For this reason, we need to generate the streamlines using the MRtrix3 package.

**Method with biological interpretation**

Univariate analysis has been performed through non-parametric statistical tests: Mann-Whitney U rank, Kruskal-Wallis and Barnard exact tests. Multivariate analysis has been performed by a Sequential Feature Selector (SFS) to select the best classifying set of microstructural metrics. The approximation of the scores has been computed through a Leave One Out Cross Validation.

**Radiomic method**

The extraction of Radiomics features has been conducted to get more informative characteristics about the shape and voxel intensities of the selected regions [10]. Radiomics features were computed by using the PyRadiomics package. Pyradiomics give the possibility to apply different filter transformations to the volumes, including wavelet and image gradient filters. Feature selection like univariate and multivariate filtering together with SFS algorithms were applied to reduce the dimensionality of the classification problem. Logistic Regression, Support Vector Machine, k-Nearest Neighbors, Multi Layer Perceptron (MLP) and Gaussian Naive Bayes algorithms have been trained to classify the patients.

**Deep Learning method**

One of the main problems of classifying NR from R patients was defining the ROI or the tract to look for any change in a metric. Deep learning is a solution to this problem since it does not need a ROI, but through training, it can learn where to see to distinguish between the two classes.

The management of volumes was done through the library TorchIO. It is an open-source library for efficient loading, preprocessing, augmentation and patch-based sampling of 3D medical images in deep learning.

To model our classification model the MONAI framework was used. MONAI is a PyTorch-based, open-source framework for deep learning in healthcare imaging, part of the PyTorch Ecosystem. The weights of a pre-trained UNEST model [11] for volumetric brain segmentation with T1 images from MONAI Model Zoo were chosen for our study. To change the model behaviour from segmentation to classification, we cut the U-shape in the point between the encoder and decoder sections, where the spatial information is reduced, and the feature information is increased. We continue the reduction by adding a non-pre-trained 3D convolution block with dropout and ReLU activation. After, a flatter transformation is applied followed by a fully connected linear layer that takes as input 2048 features and returns a single output value for binary classification.

**Results**

Treatment in NR demonstrated a greater MD in the thalamocortical connections, the fornix, and the anterior commissure ($p < 0.01$). As well as the feature selector, in a multivariate analysis the fornix being the most frequent region selected by the SFS, followed by the Accumbens Area.

In Radiomics analysis Wavelet and local binary pattern features have been the most frequently selected, reaching an accuracy above 0.9 in Logistic Regression, Gaussian Naive Bayes and MLP models. The ensemble model given by the fusion of the two best Gaussian models reached an accuracy and Area Under the ROC (AUC) curve of 1 in our dataset.

Expected results have been found with deep learning approaches, overfitting has been observed due to the lack of a large dataset. The training set reached an accuracy and AUC of 1 while the validation set had an accuracy of 0.7 and an AUC score of 0.85, these results were obtained using a batch size of 16, a learning rate equal to 0.0001 with a decay of 0.01 every 7 epochs in an AdamW optimizer. The size of the training and validation set was augmented with a multiplier factor of 20 times the original size.

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