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

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Epilepsy

Epilepsy is a neurological disorder characterized by recurrent and unpredictable seizures.

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Seizures can be focal or generalized.

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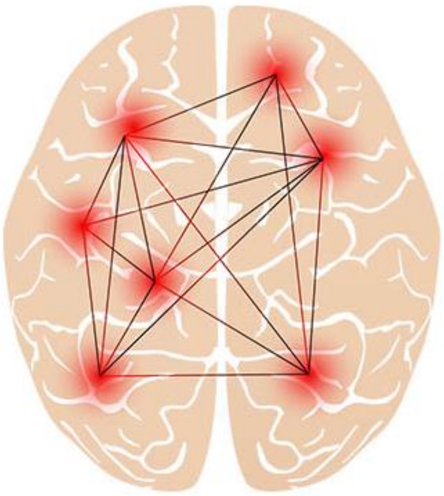
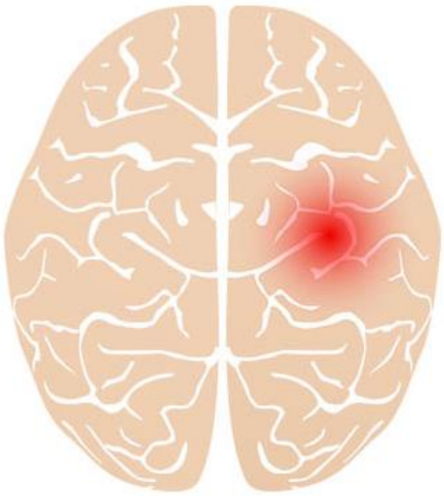


Generalized Seizure



Focal Seizure

Epilepsy

Epilepsy is a neurological disorder characterized by recurrent and unpredictable seizures.

An epileptic seizure is an abnormal excitation or inhibition of electrical activity within the neural network, that may lead to convulsions and loss of awareness.
Seizures can be focal or generalized.

Treatments for epilepsy typically involves medications, but in cases of drug-resistant patients, other treatments such as surgery and neurostimulation therapies can be considered

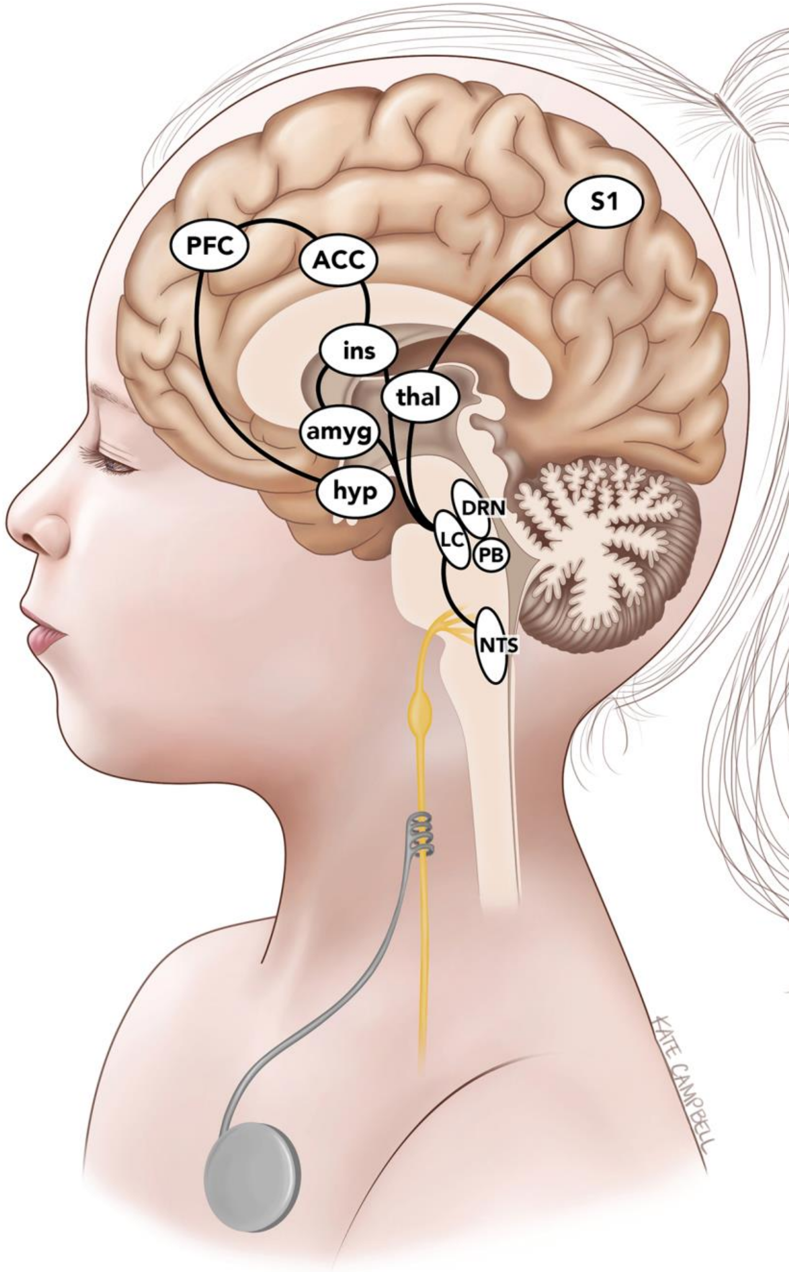
Vagus Nerve Stimulation (VNS) is one of the many neurostimulation therapies that can be used when surgery is not possible.

Vagus Nerve Stimulation

The exact mechanism by which VNS reduces seizures is not fully understood.

Responders (R) to VNS will be defined as those who experience a reduction >50% in seizure frequency after VNS, partial responders (PR) who experience a reduction between 30% and 50% and non-responders (NR) who experience a reduction <30%.

Clinical trials prove that after 24 to 48 months after the implantation of the device, 60% of the patients were considered responders and 8% were seizure-free.



Question

Is it possible to find brain microstructures that predict VNS response?

Previous studies

A scoping review of litterature has been done in 2020 by *Workewych* to identify biomarkers of VNS response in drug-resistant epilepsy patients.

Ibrahim in 2017 through a resting-state functional MRI observed an higher thalamocortical connectivity involving the insula and anterior cingulate cortex in reponders compared to non-responders.

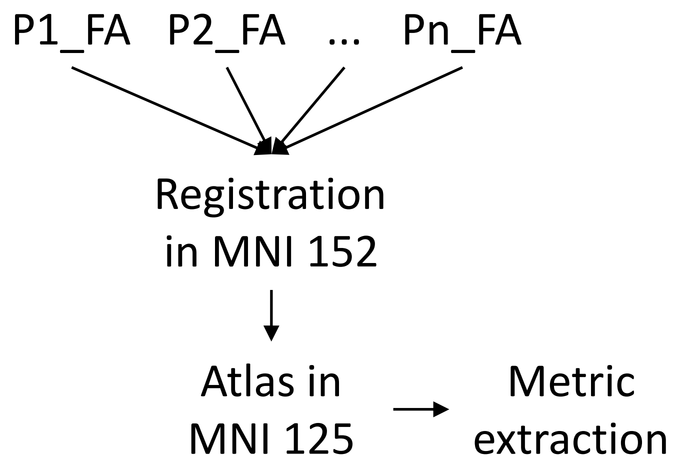
A study done in 2019 by *Mithani* using diffusion MRI demonstrated differences between responders and non-responders of Fractional Anisotropy (FA) in the left-lateralized posterior thalamic radiation, fornix and association fibres.

Previous studies

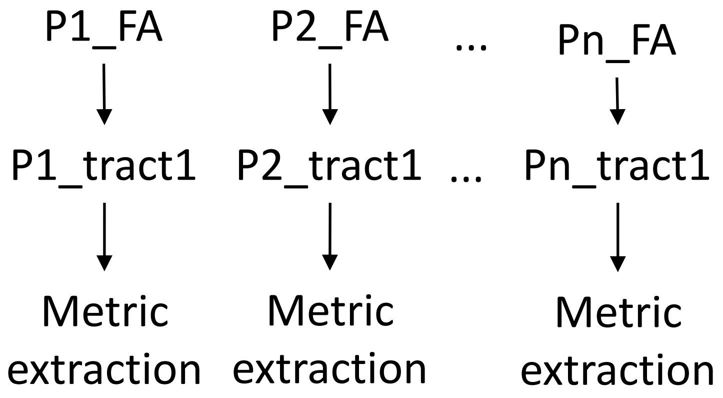
Limitations of *Mithani* study:

- Region of Interest (ROI) are defined using a Tract-Based Spatial Statistics analysis.
- Only DTI metrics were used to build the classifier

TBSS

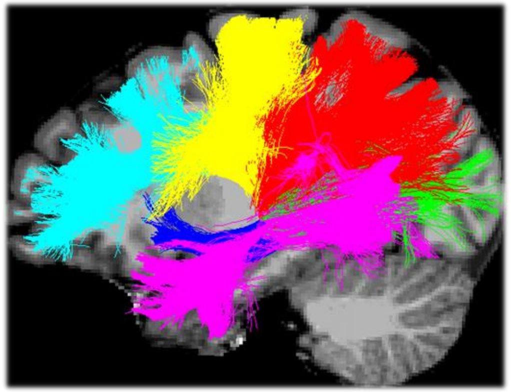


Our study



Objective

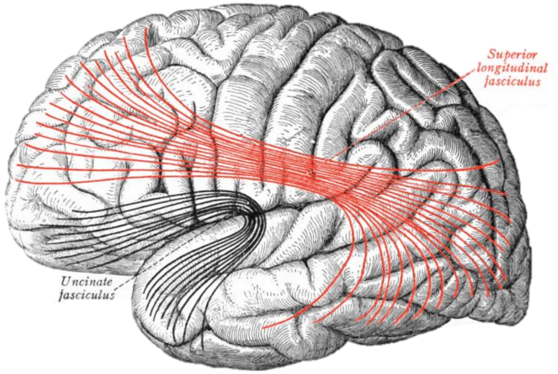
- Use a tractography approach to extract the metrics without registering the diffusion image.
- Use of multi-compartment models (NODDI, DIAMOND, MF) which overcome the problems of the DTI model and have more interpretability.

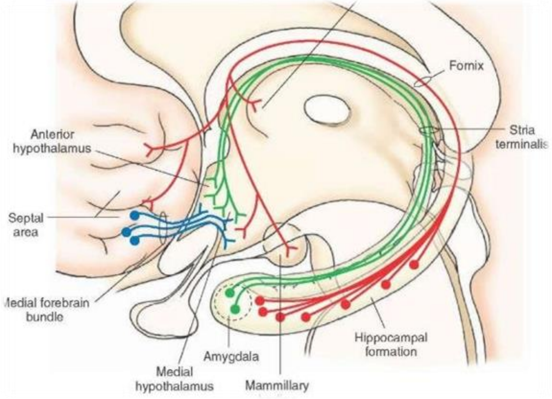


Hypothesis

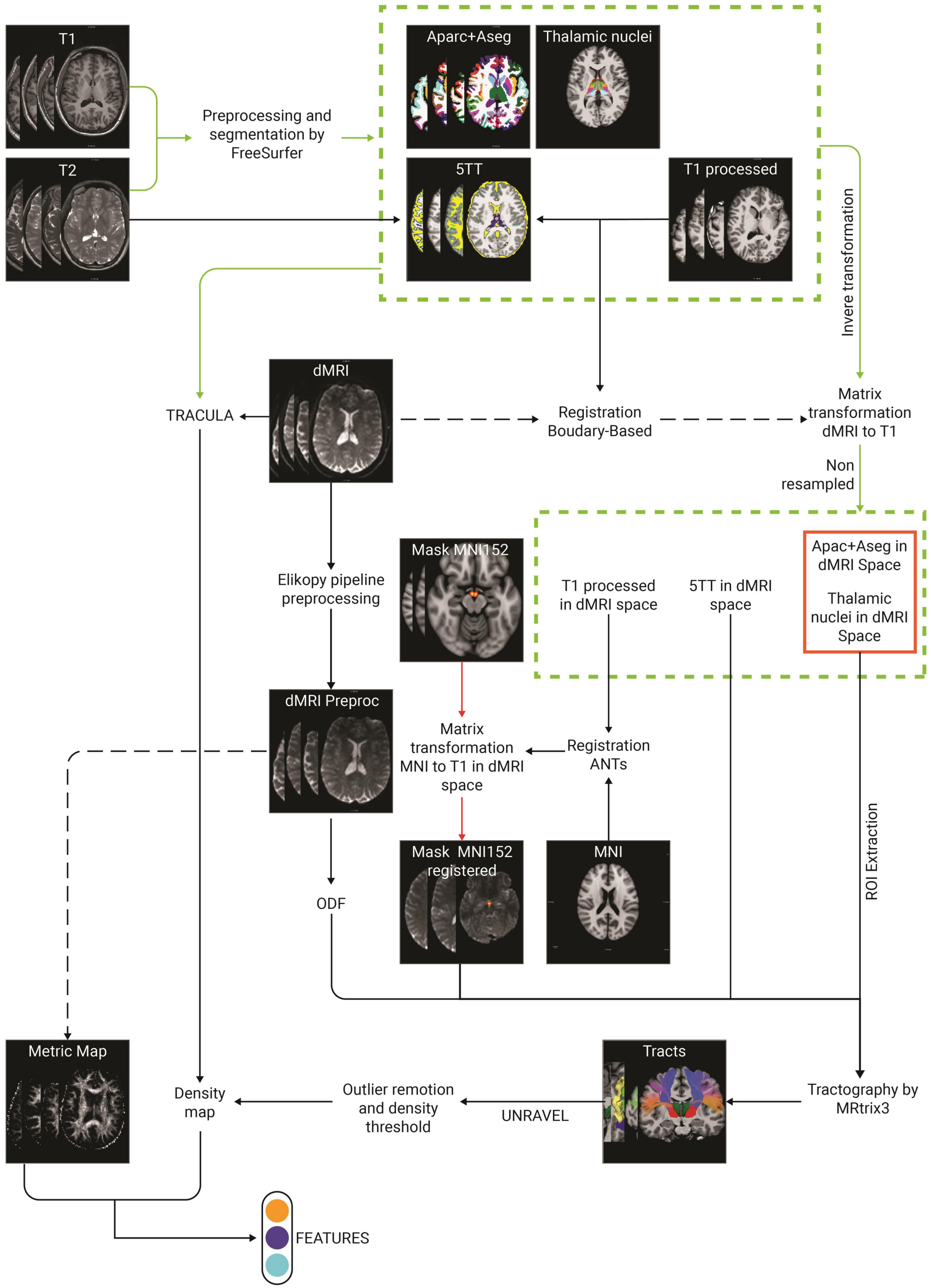
Differences in microstructures are expected in:

- Thalamocortical radiation
- Limbic system
- Association fibres

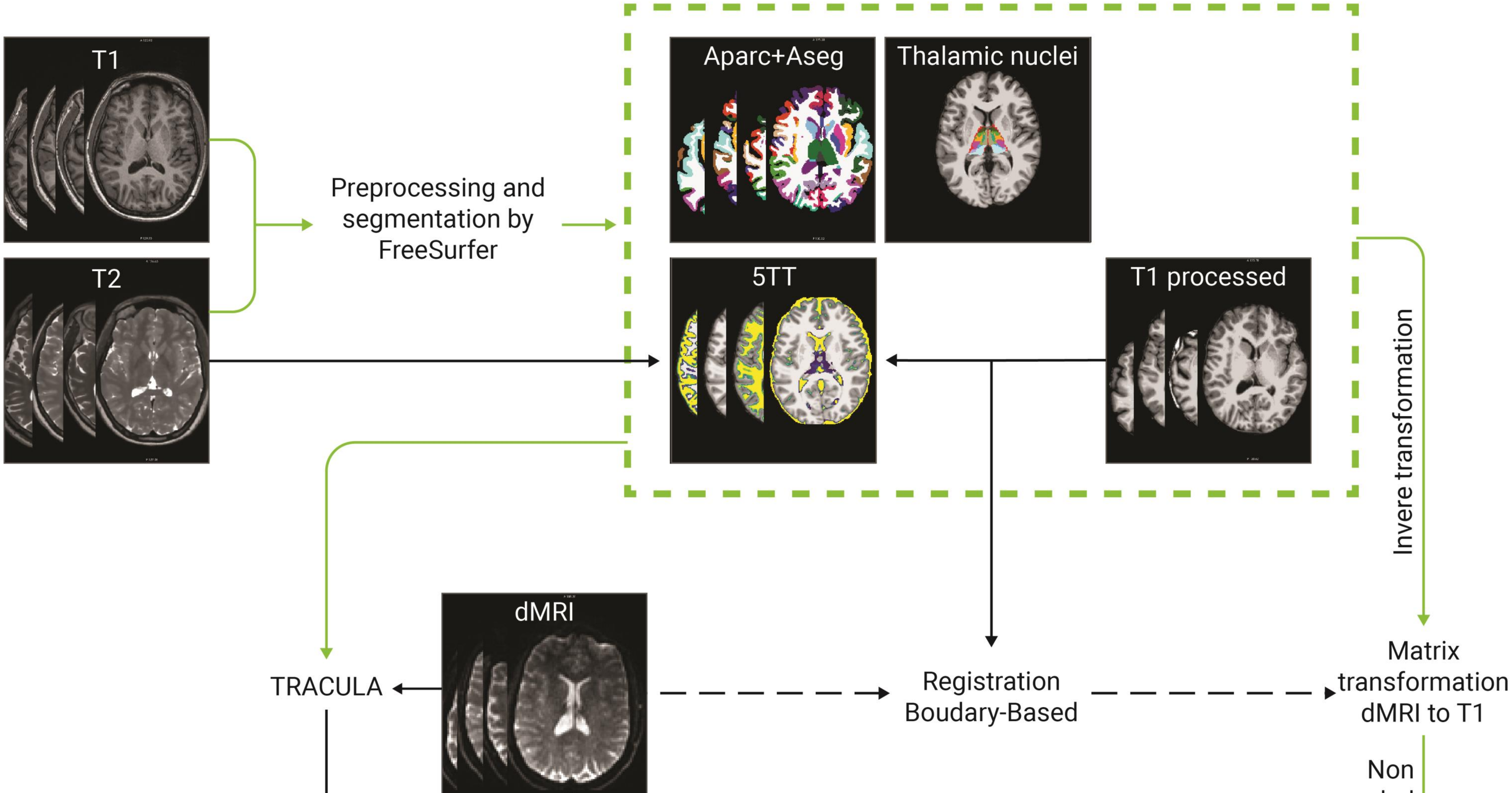




Method


T1
T2
Preprocessing and segmentation by FreeSurfer
Aparc+Aseg
Thalamic nuclei
5TT
T1 processed
Invere transformation
dMRI
TRACULA
Registration Boudary-Based
Matrix transformation dMRI to T1
Non resampled
Elikopy pipeline preprocessing
Mask MNI152
T1 processed in dMRI space
5TT in dMRI space
Apac+Aseg in dMRI Space
Thalamic nuclei in dMRI Space
dMRI Preproc
Matrix transformation MNI to T1 in dMRI space
Registration ANTs
ROI Extraction
ODF
Mask MNI152 registered
MNI
Metric Map
Density map
Outlier remotion and density threshold
UNRAVEL
Tracts
Tractography by MRtrix3
FEATURES

Method



T1
T2
Preprocessing and segmentation by FreeSurfer
Aparc+Aseg
Thalamic nuclei
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T1 processed
Invere transformation
dMRI
TRACULA
Registration Boudary-Based
Matrix transformation dMRI to T1
Non

Method

Subjects

The study was composed of 19 subjects with drug-resistant epilepsy.

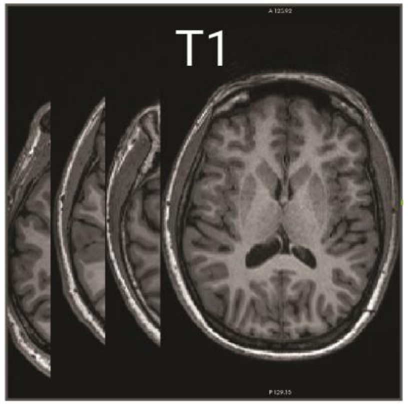
- 8 Responders
- 4 Partial responders
- 7 Non-responders

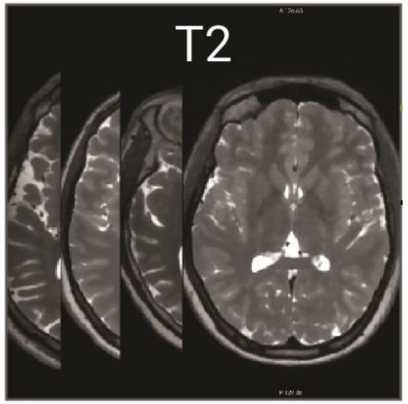
Data acquisition

For each subjects were acquired:

- T1-anatomical images
- T2-weighted images
- Diffusion weighted MRI images
  - 64 gradients at bval=0, 1000, 2000, 3000, 5000

Volumes were in DICOM format and converted in NIfTI

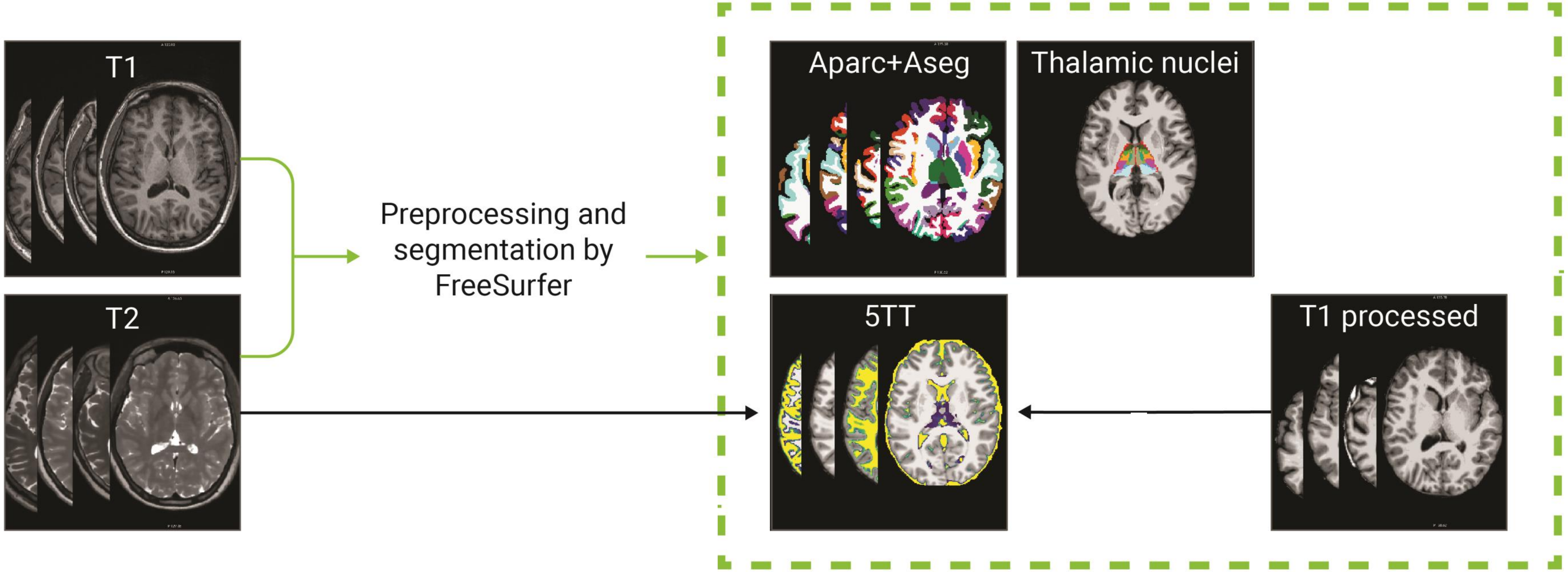




Anatomical images preprocessing

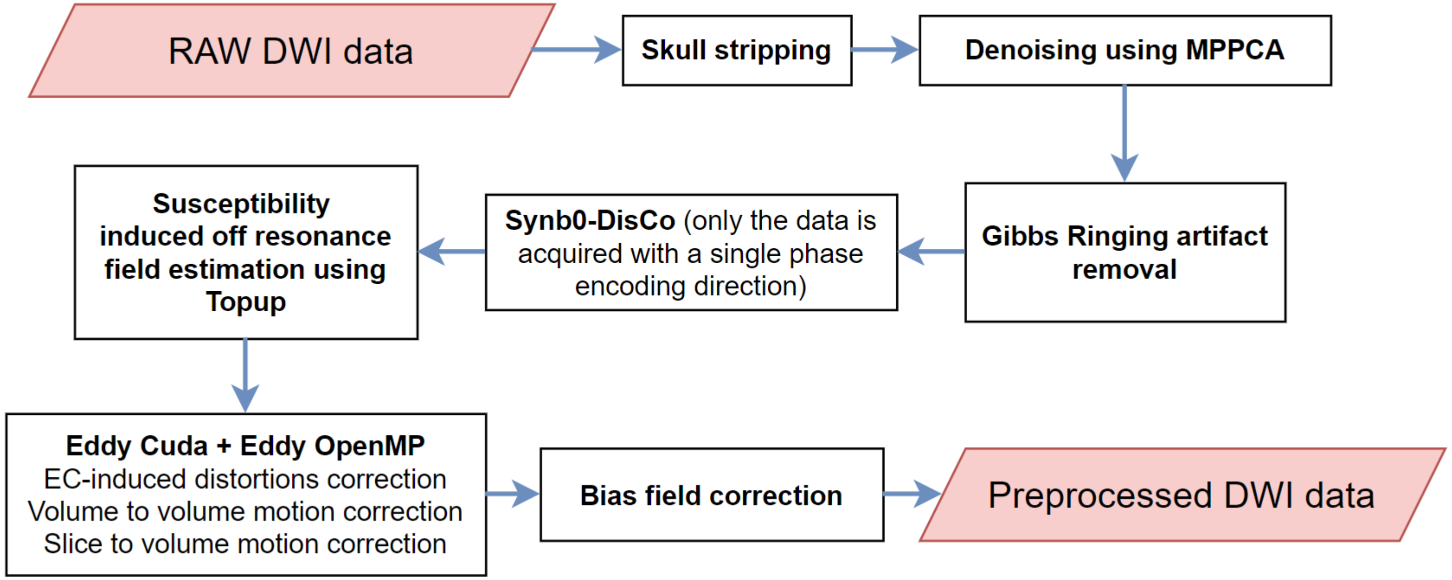
The preprocessing steps done on T1 image are:

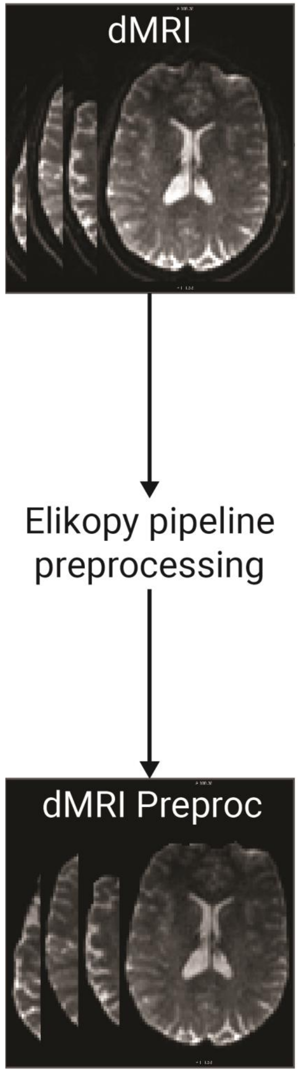
- Motion correction
- Intensity normalization
- Skull-tripping



Elikopy Pipeline

DW-MRI images were preprocessed using the Elikopy pipeline.

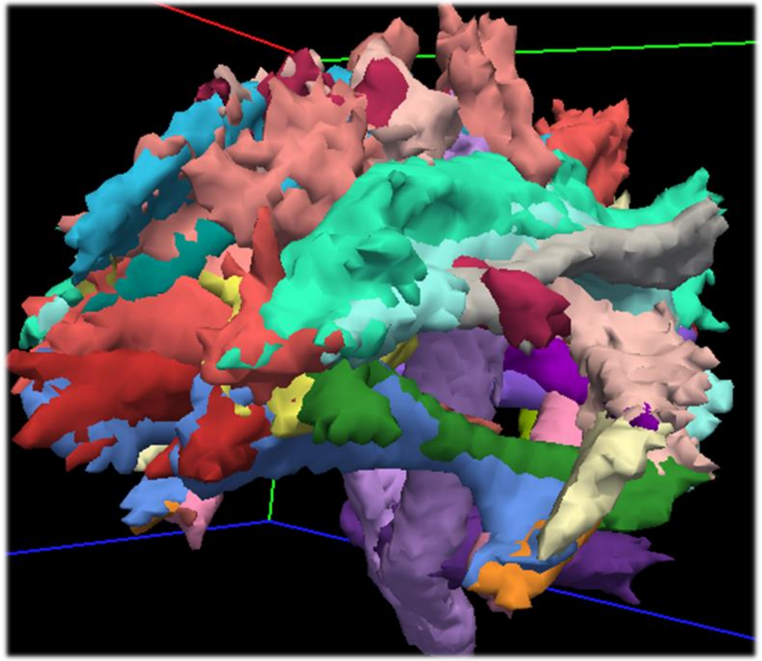


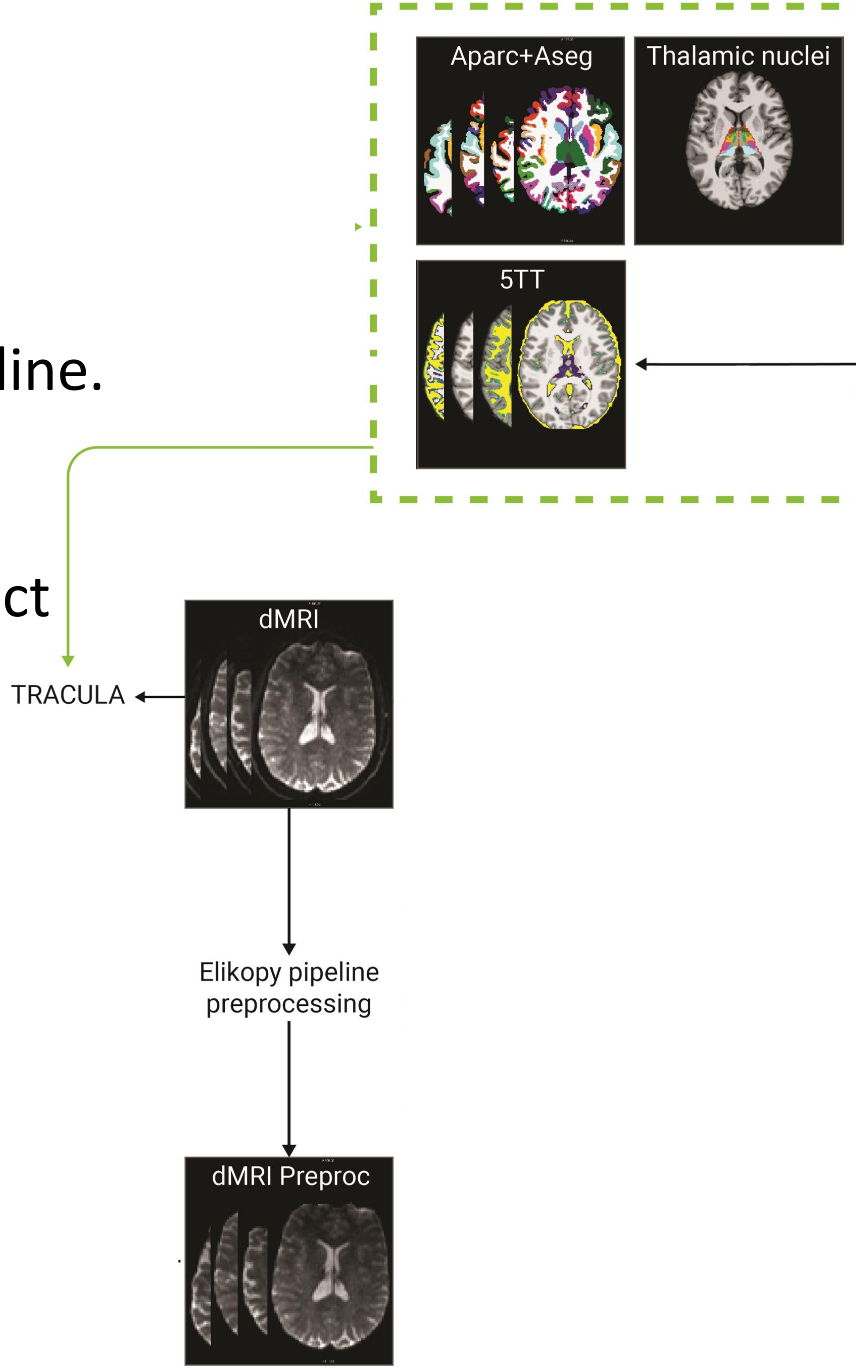


FreeSurfer Tracts extraction

DW-MRI images were preprocessed using the Elikopy pipeline.

After the preprocessing, the dMRI images are given to FreeSurfer together with the segmentations and all the tract regions are computed for each subjects.





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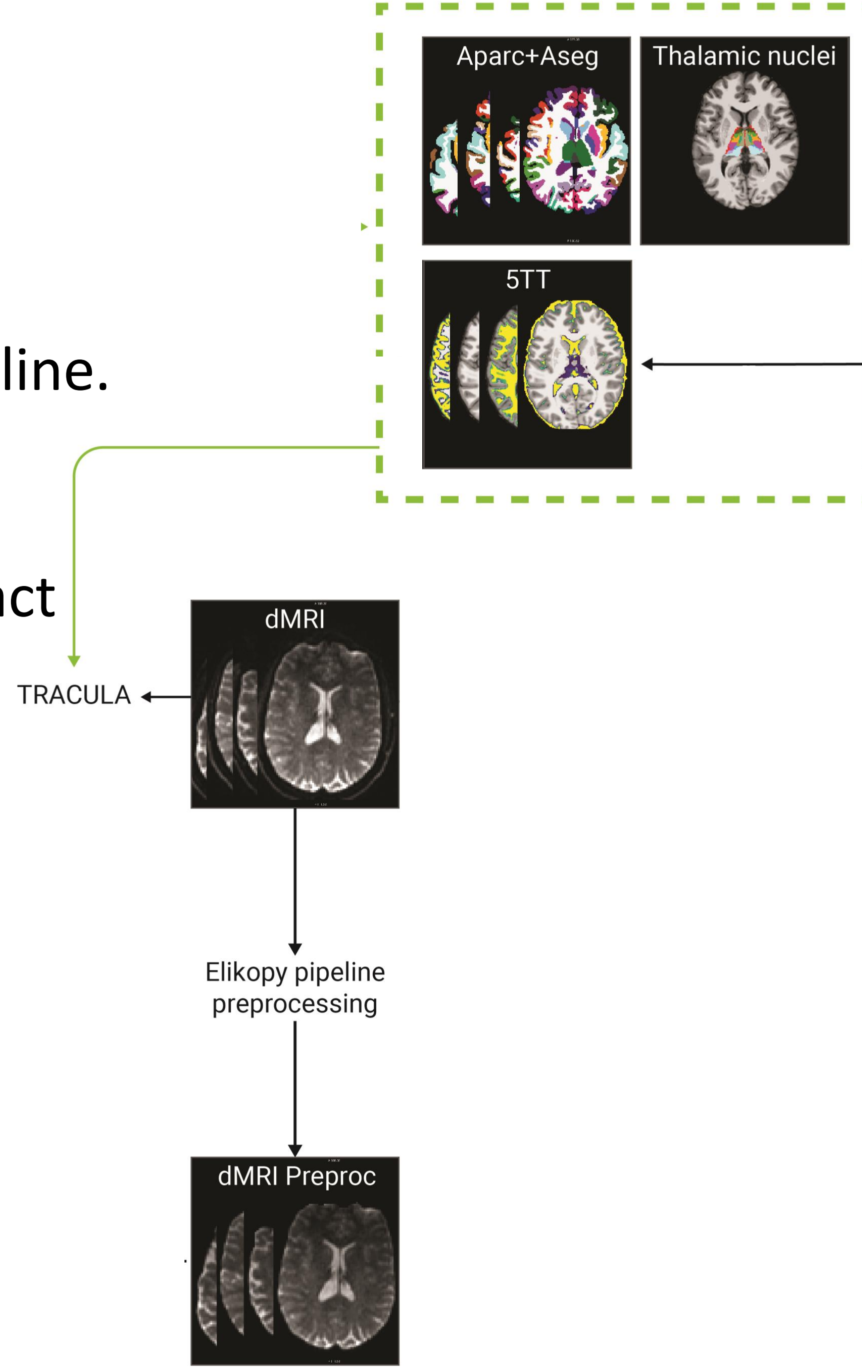
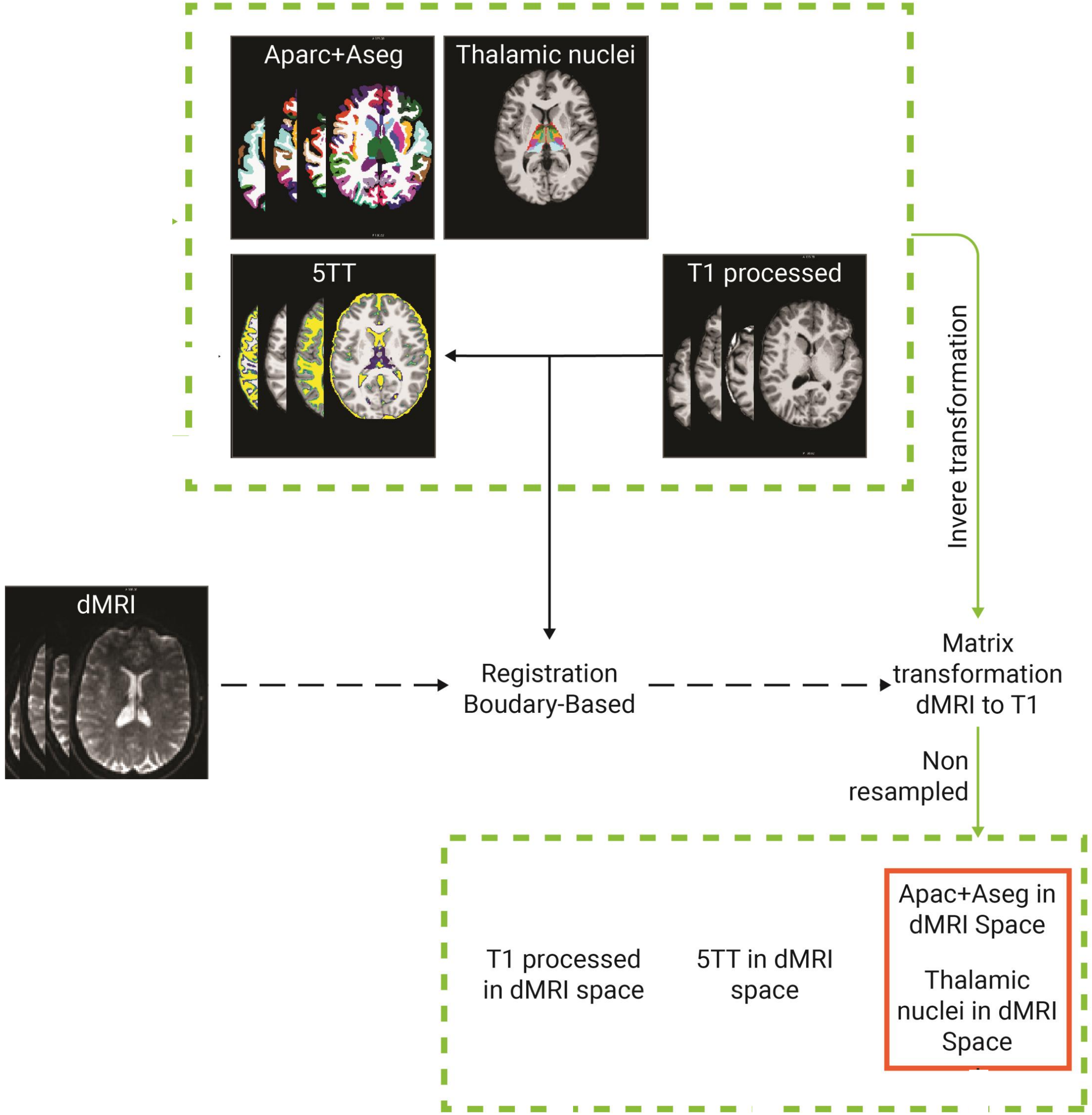
FreeSurfer does not compute the tracts of:

- Posterior thalamocortical radiation
- Superior thalamocortical radiation
- Inferior thalamocortical radiation

Therefore, non-automatized software as MRtrix3 is used to compute the remaining tracts.



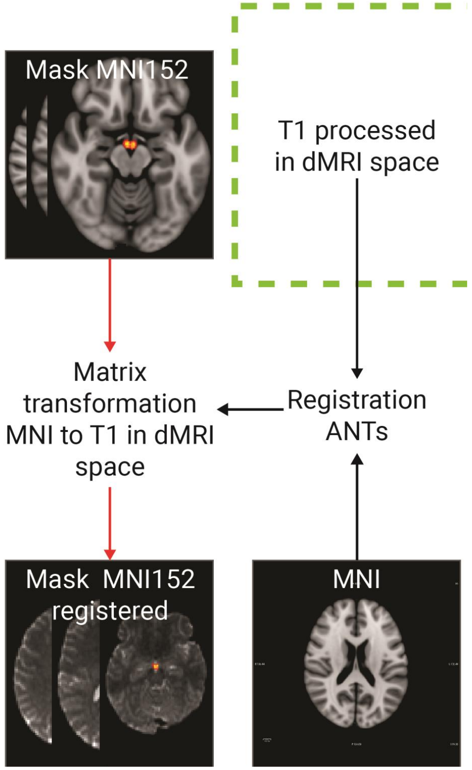


Registration

Diffusion images are not registered in a common space to avoid interpolation of the intensities. The metric extraction is done in the dMRI space.

T1 images and their products such as the segmentations and 5TT must be registered in the diffusion space.

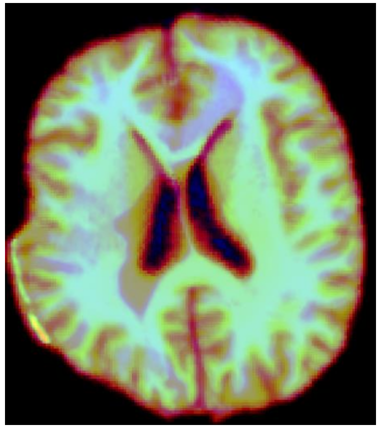
Boundary-Based Registration
without resampling

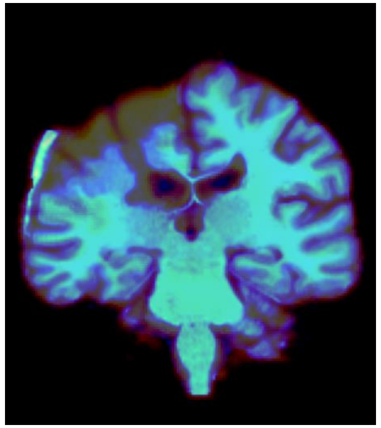


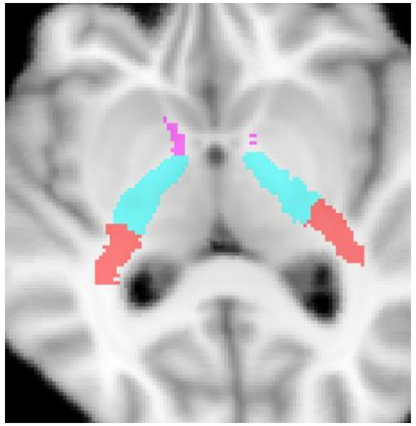
Registration

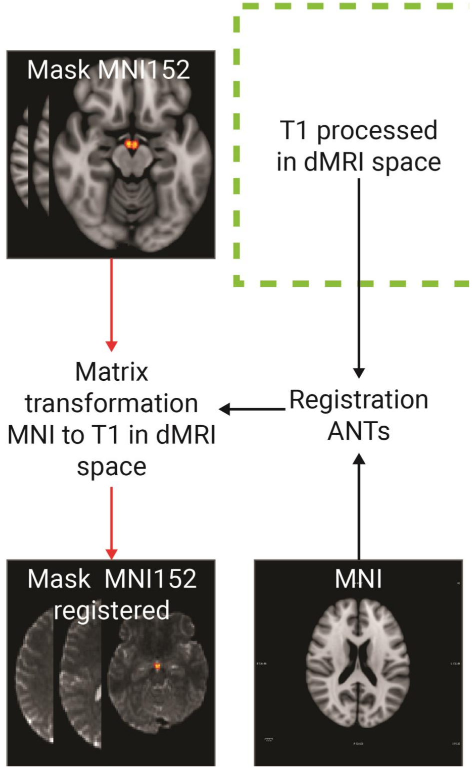
The missing ROIs non extracted by FreeSurfer are extracted from the Atlases in MNI 152 space.

Then they are registered in the diffusion space through a non-linear symmetric normalization transformation.









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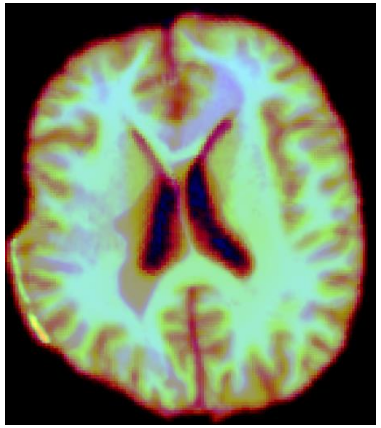
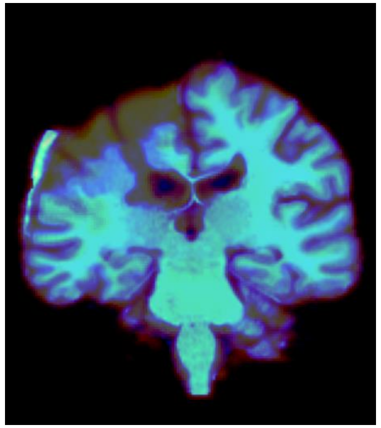
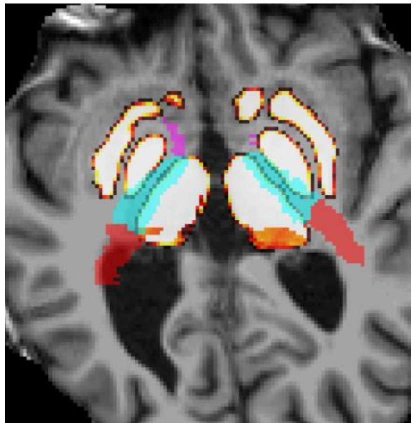
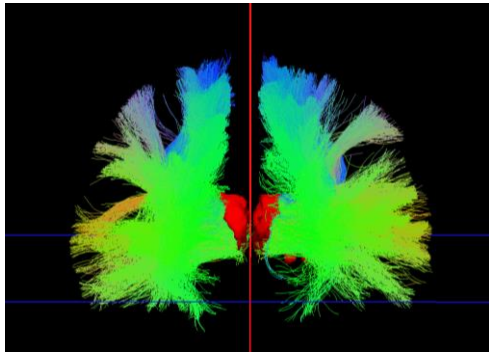


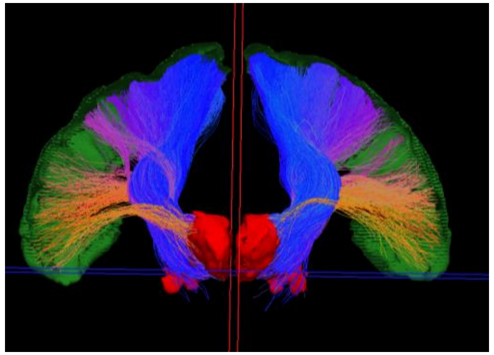




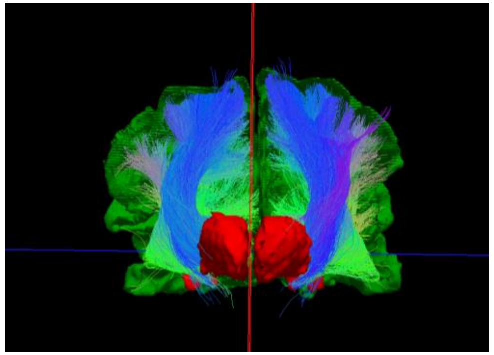
MRtrix3 Tractography



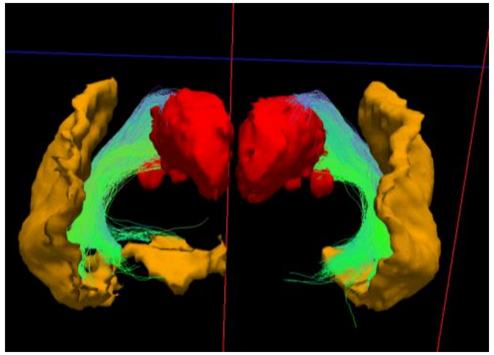
Anterior Thalamocortical Radiation



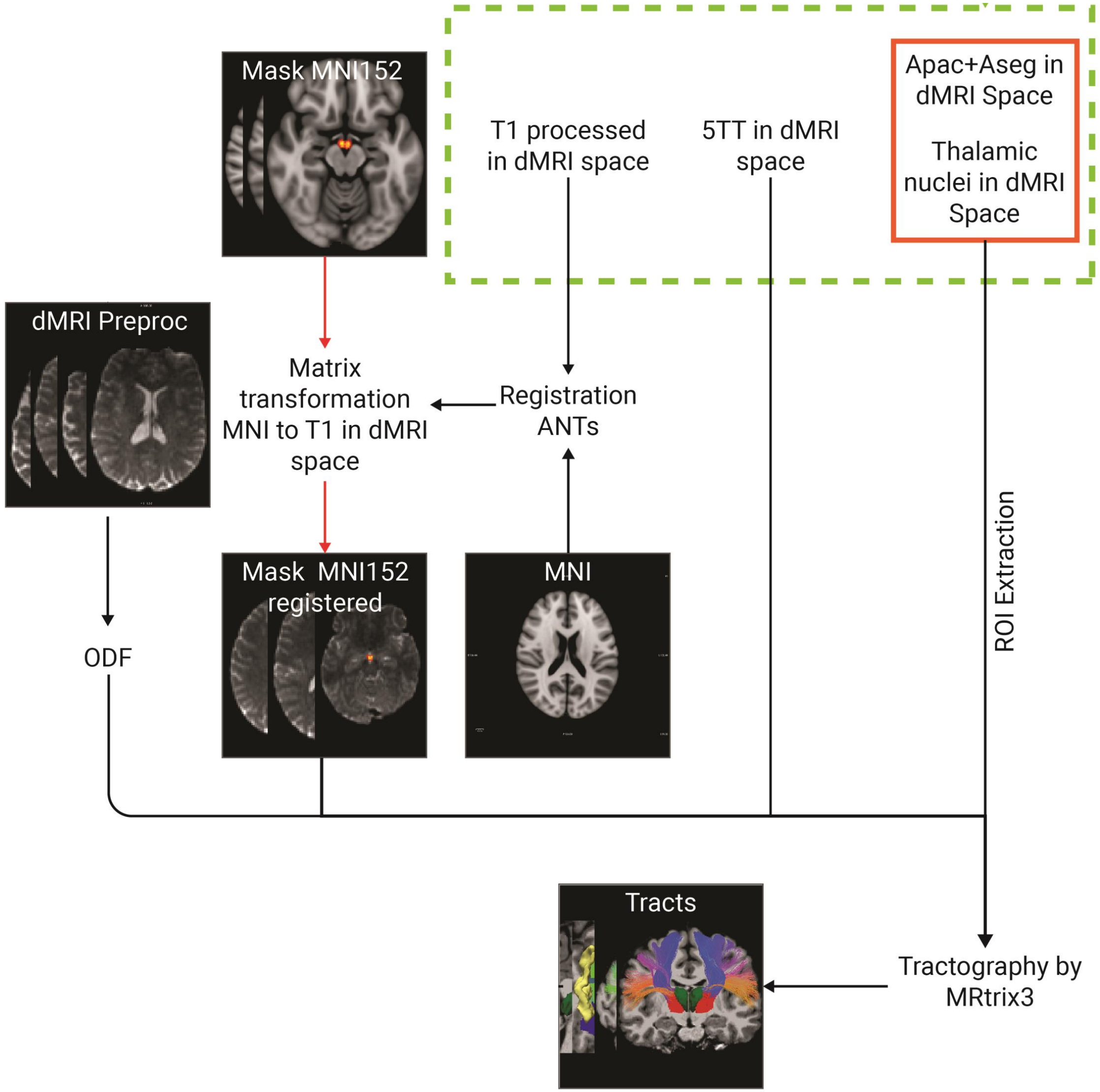
Superior Thalamocortical Radiation



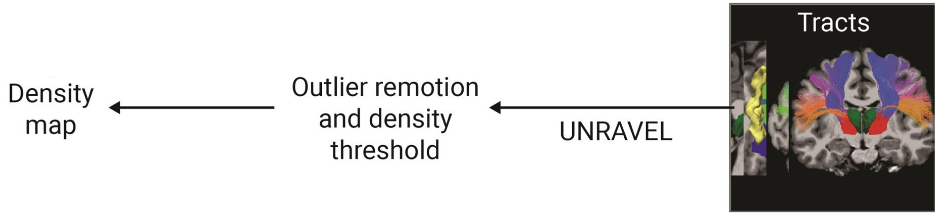
Posterior Thalamocortical Radiation



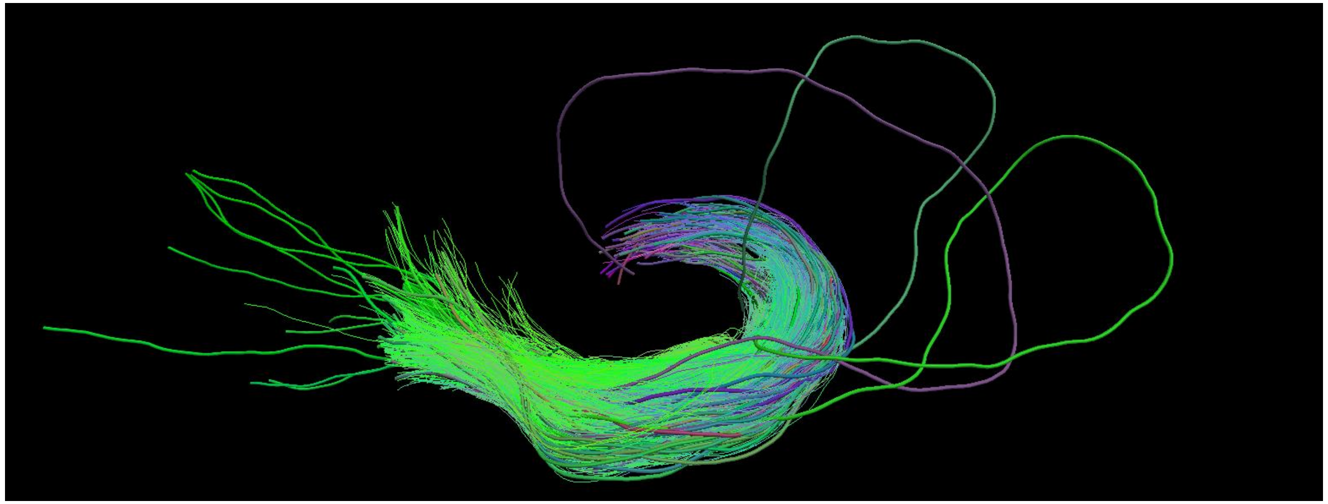
Thalamus to Insular cortex radiation



ROI extraction from tracts

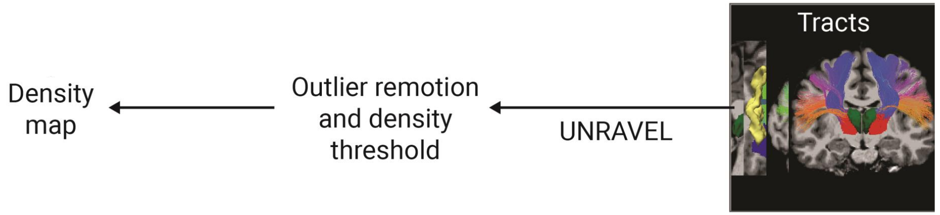


Streamlines that are too long or too short compared to the rest of the fascicle are considered outliers.
Inter Quartile Range (IQR) rule is used to remove these outliers.



Example of the thalamus to insular cortex tract

ROI extraction from tracts



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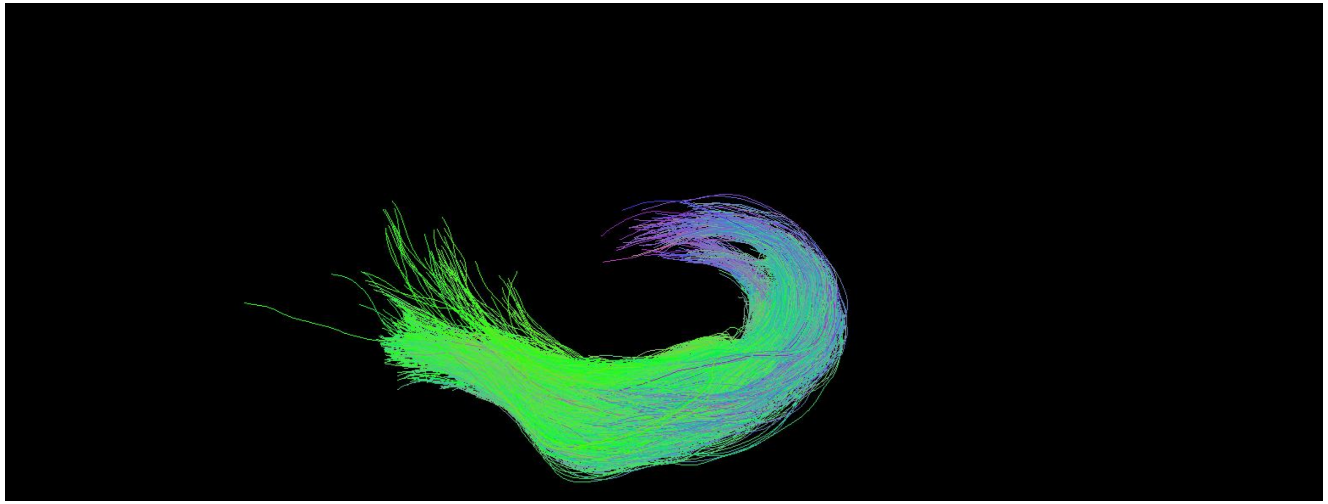
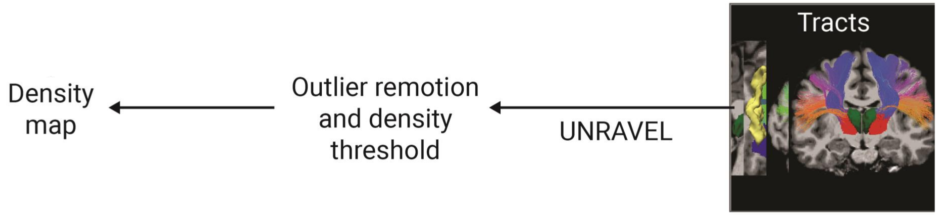


Example of the thalamus to insular cortex tract

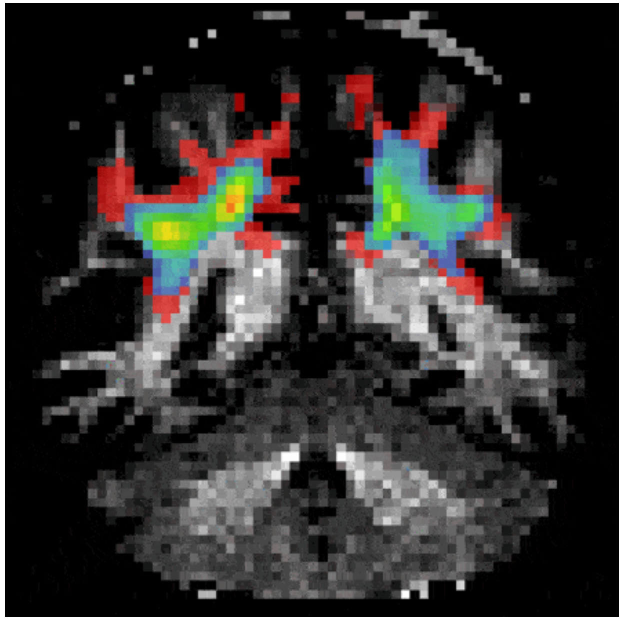
ROI extraction from tracts



Streamlines that are too long or too short compared to the rest of the fascicle are considered outliers.
Inter Quartile Range (IQR) rule is used to remove these outliers.

The probabilistic tracts are converted in a density map through the library UNRAVEL.

To keep only the main pathway and the voxels with the highest probability a Gaussian filter is applied, and the voxels greater than a threshold are kept.

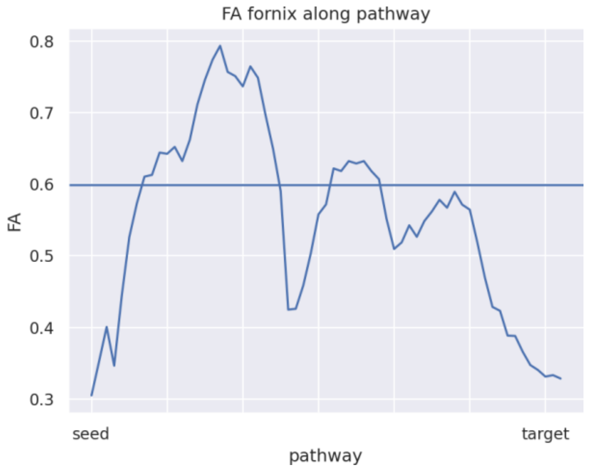


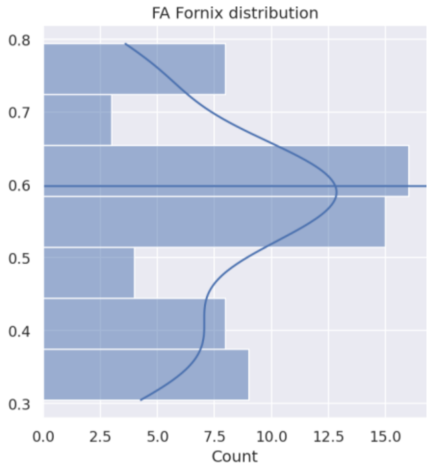
Example of SLF

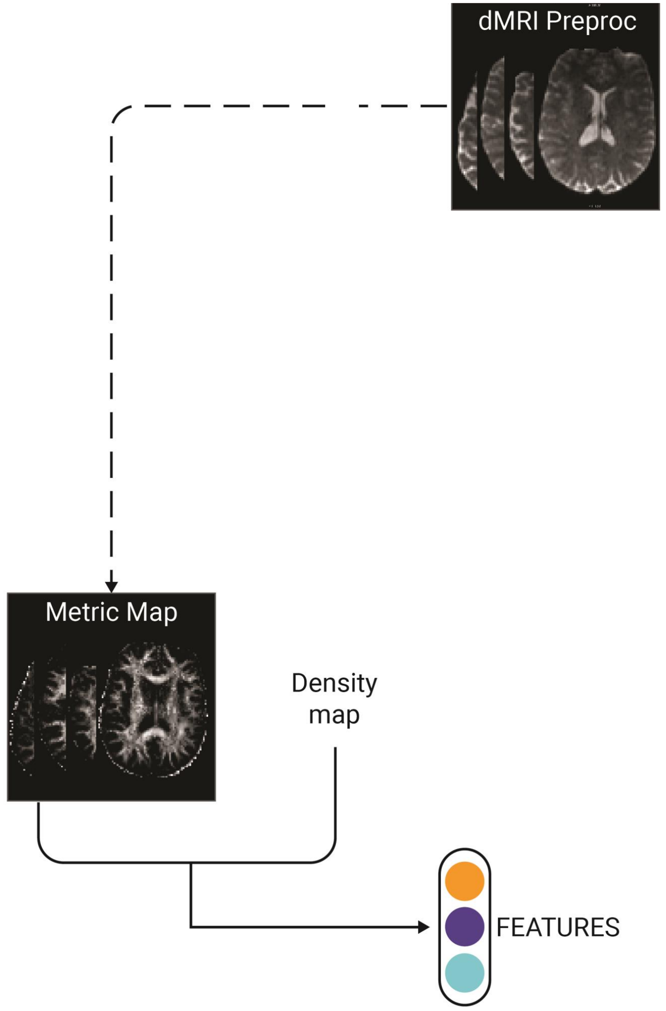
Metric extraction from ROIs

Each tract has a distribution of the metric value in the region.
We have computed the weighted mean, standard deviation, skewness and kurtosis to fully represent the distribution.

For the regions taken from the tracts same terms are computed, but the interpretation is different.







Automation of the extraction without TRACULA

The extraction process of the metric extraction without using TRACULA, but MRtrix3, was written in python. The code is private on my GitHub.

The software is semi-automatic and takes as input a json file, and the T1, T2, dMRI images. It computes the metrics for all the subjects.

```
{
  “fornix”:
    {
      “seed_image”: [“plane-mammillary-body”],
      “include_orderd”: [“plane-ort-fornix”, “plane-fornix”, “hippocampus”],
      “exclude”: [“Thalamus-eroded-1”, “Lateral-Ventricle-eroded-1”],
      “angle”: 15,
      “stop”: true,
      “act”: false
    }
}
```

Statistical Analysis

Different statistical tests are used to assess differences in microstructural features between responders and non-responders to VNS:

- Mann-Whitney U rank test is used to compare two groups with continues variable
- Kruskal-Wallis test is used to compare two or more groups
- Barnard’s exact test is used to compare two groups with categorical variables

These tests are the corresponding non-parametric tests of t-test, ANOVA and Chi2.

Multiple test p-value corrections can be applied to have more statistical power.
In this study we considered statistical significative features with p-values <0.01

Classification Model

Finding the best microstructural feature able to classify the response to VNS can be achieved by using Machine Learning algorithms.

The pipeline followed was:

Scaling

- Different scaling approach were tried, and the best was chosen

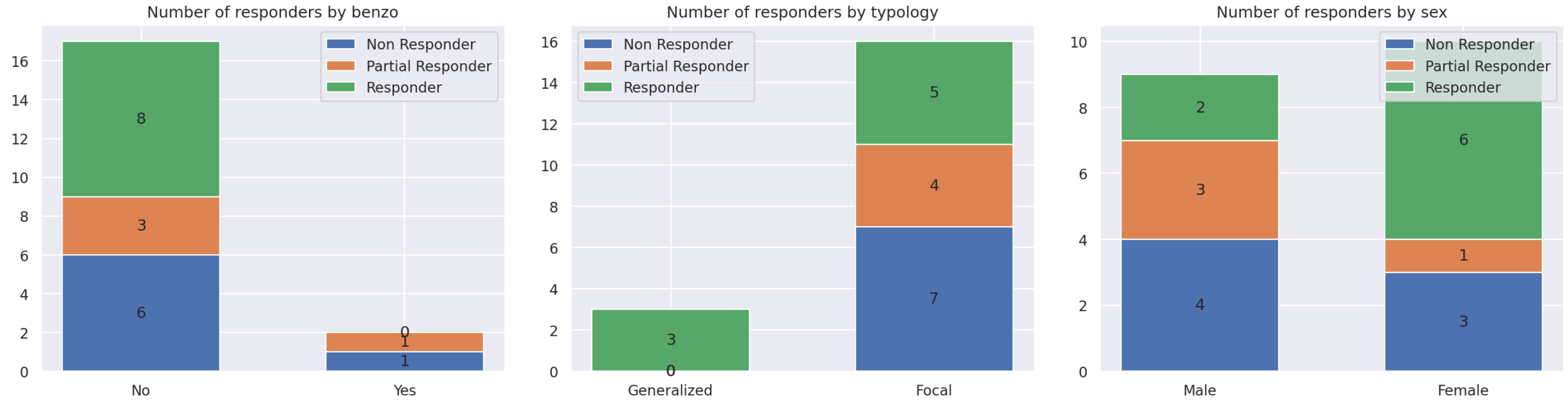
Hyperparameters Tuning (Grid Search)

- Logistic Regression
- Linear SVM
- Polynomial kernel SVM
- RBF kernel SVM

Feature Selection

- Sequential Feature Selection (SFS) was preferred to PCA or ICA, since it doesn't modify the feature space

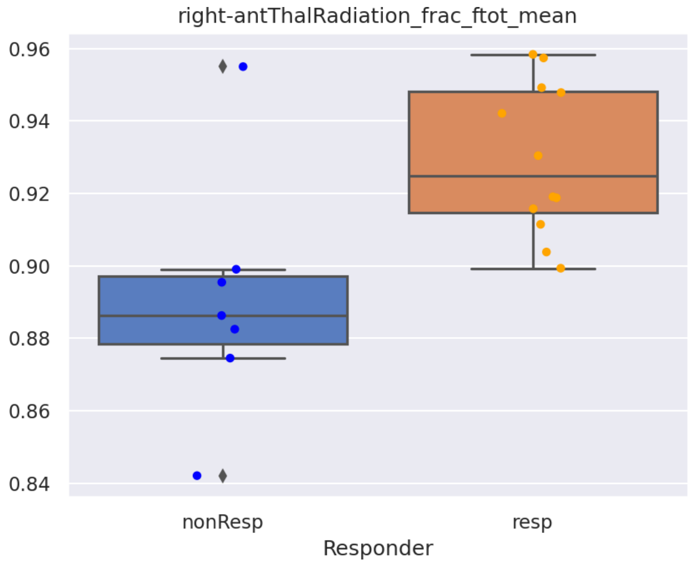
Results: Categorical Features

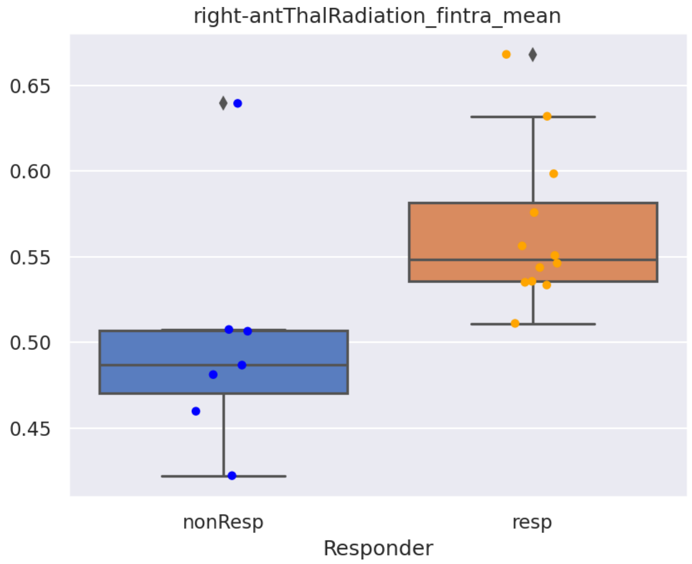


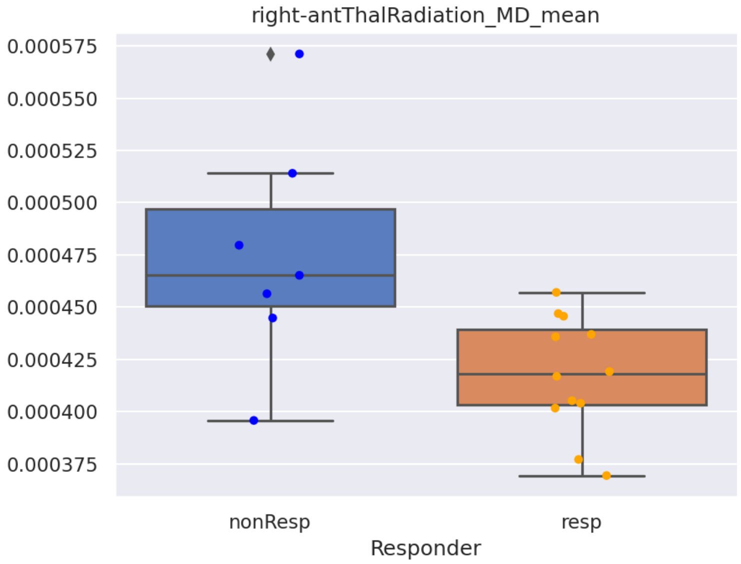
We cannot say anything about statistical dependency considering categorical features.

Results: Microstructural Features

Anterior Thalamocortical Radiation

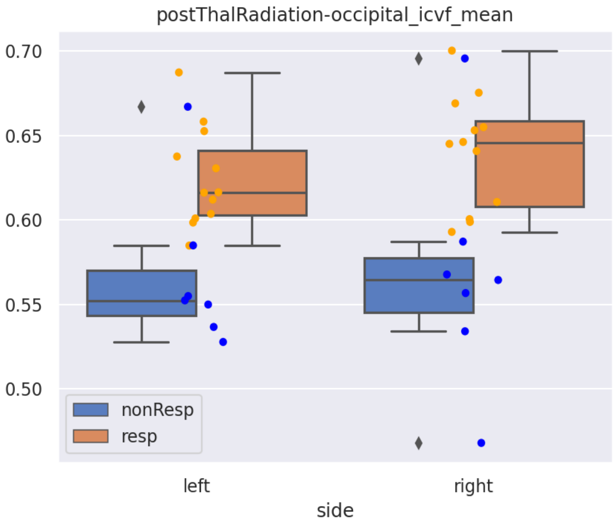


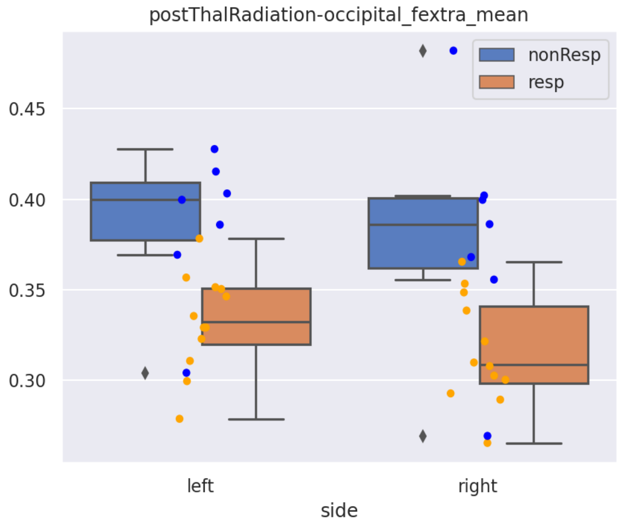


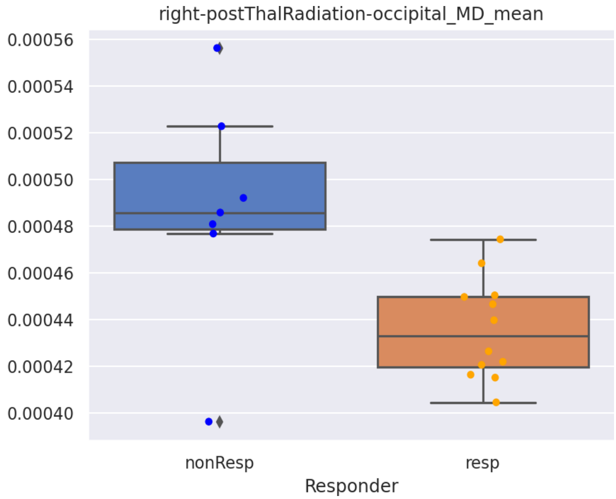


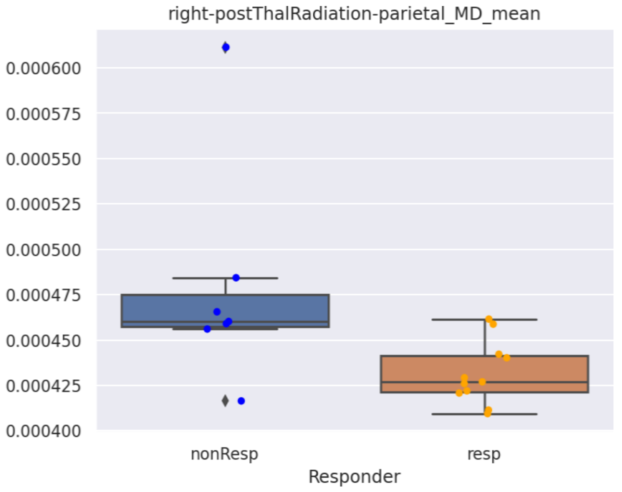
Results: Microstructural Features

Posterior Thalamocortical Radiation



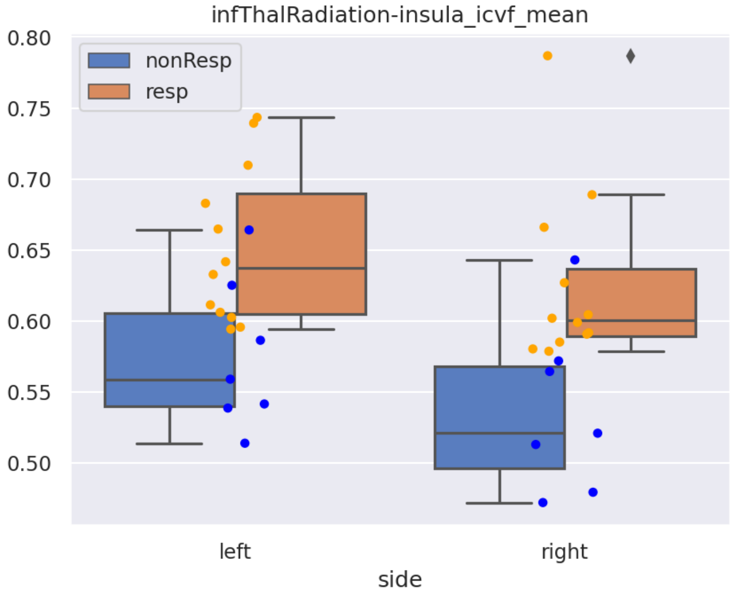


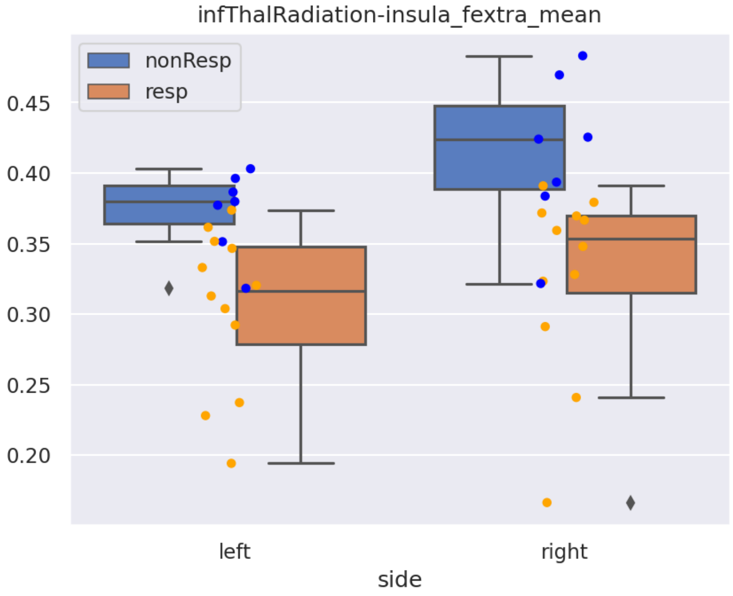


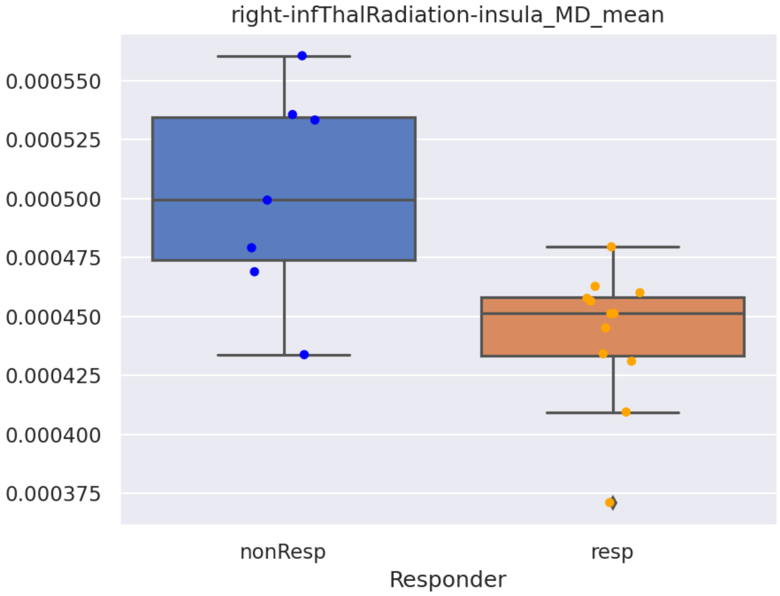


Results: Microstructural Features

Inferior Thalamocortical Radiation – Insular Cortex

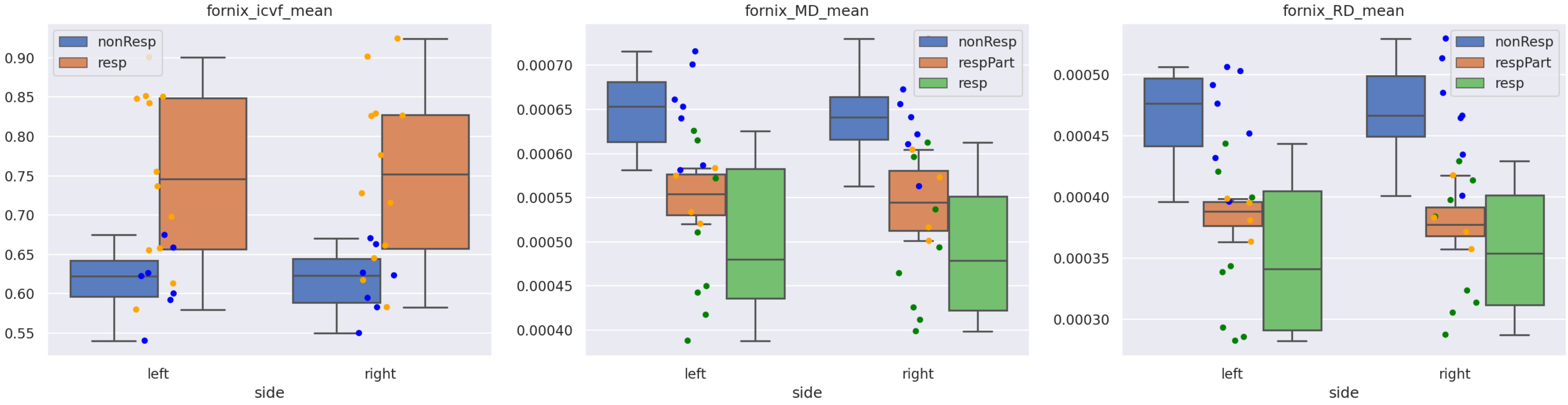






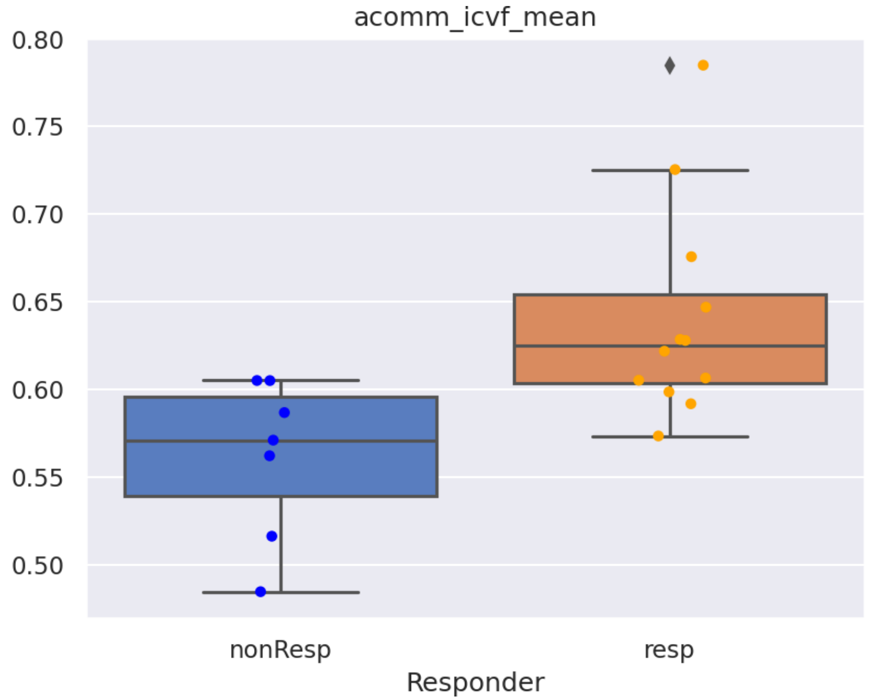
Results: Microstructural Features

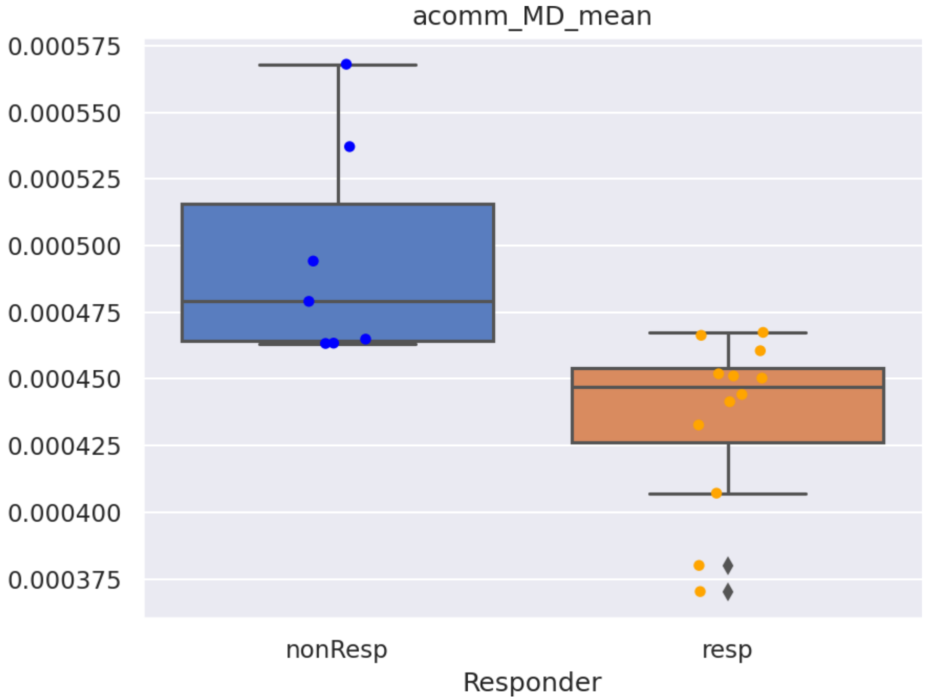
Fornix



Results: Microstructural Features

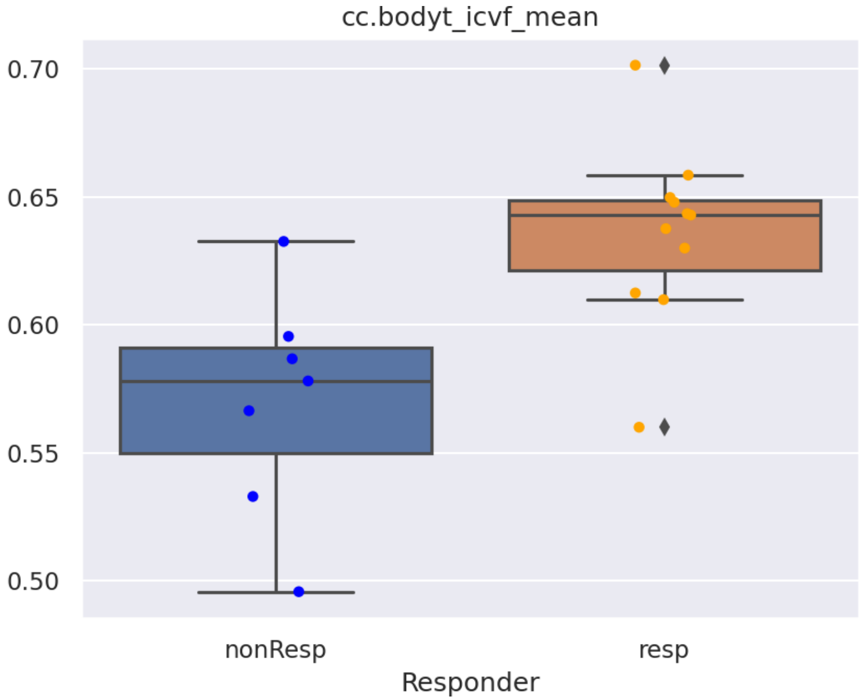
Anterior Commissure

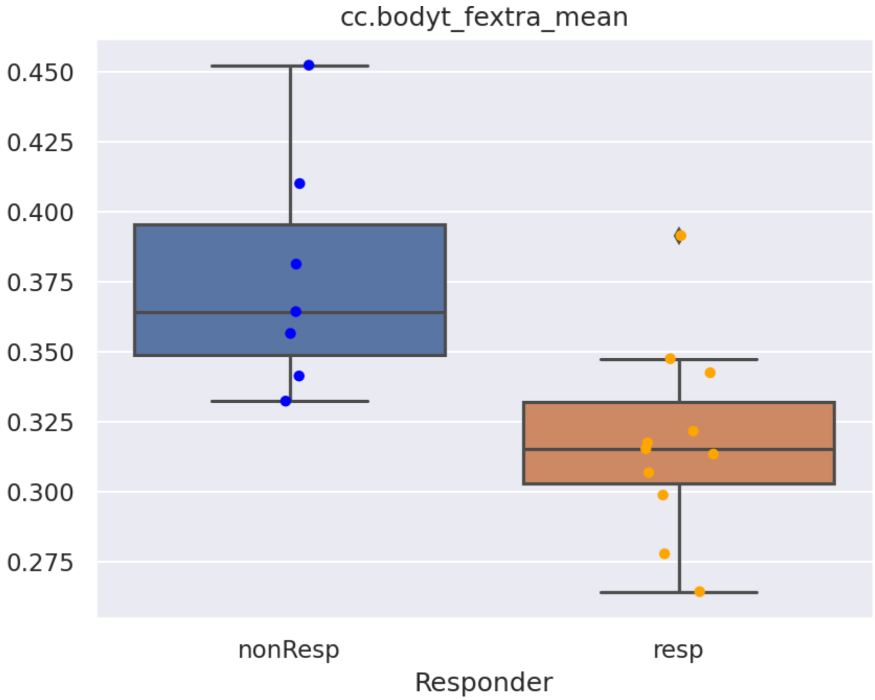




Results: Microstructural Features

Temporal body of the corpus callosum



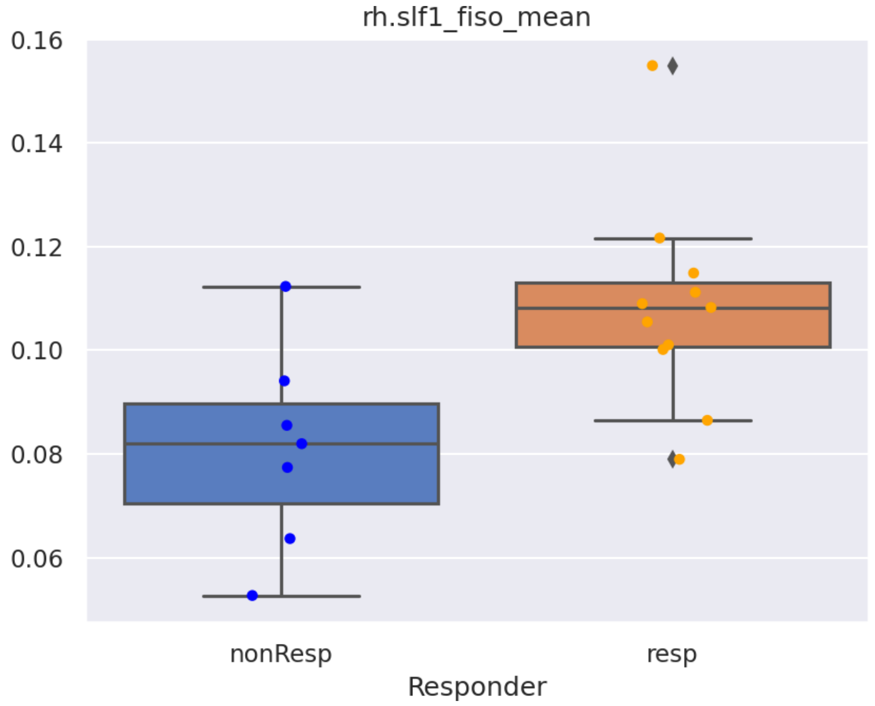


Results: Microstructural Features

Superior Longitudinal Fasciculus I

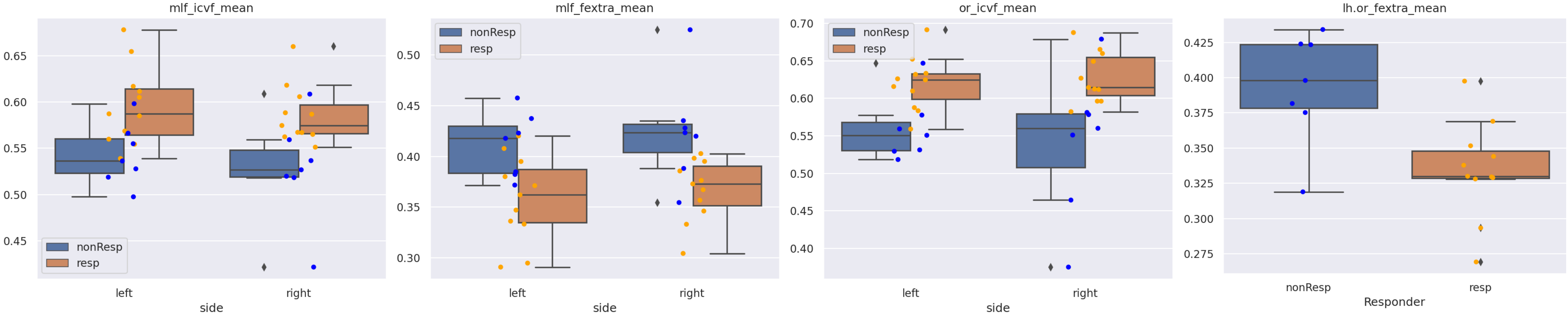
Having a decrease of CSF means having an increase of fibre fraction.

It is in contrasts with the results of Mithani where NR had a reduction of axonal integrity.

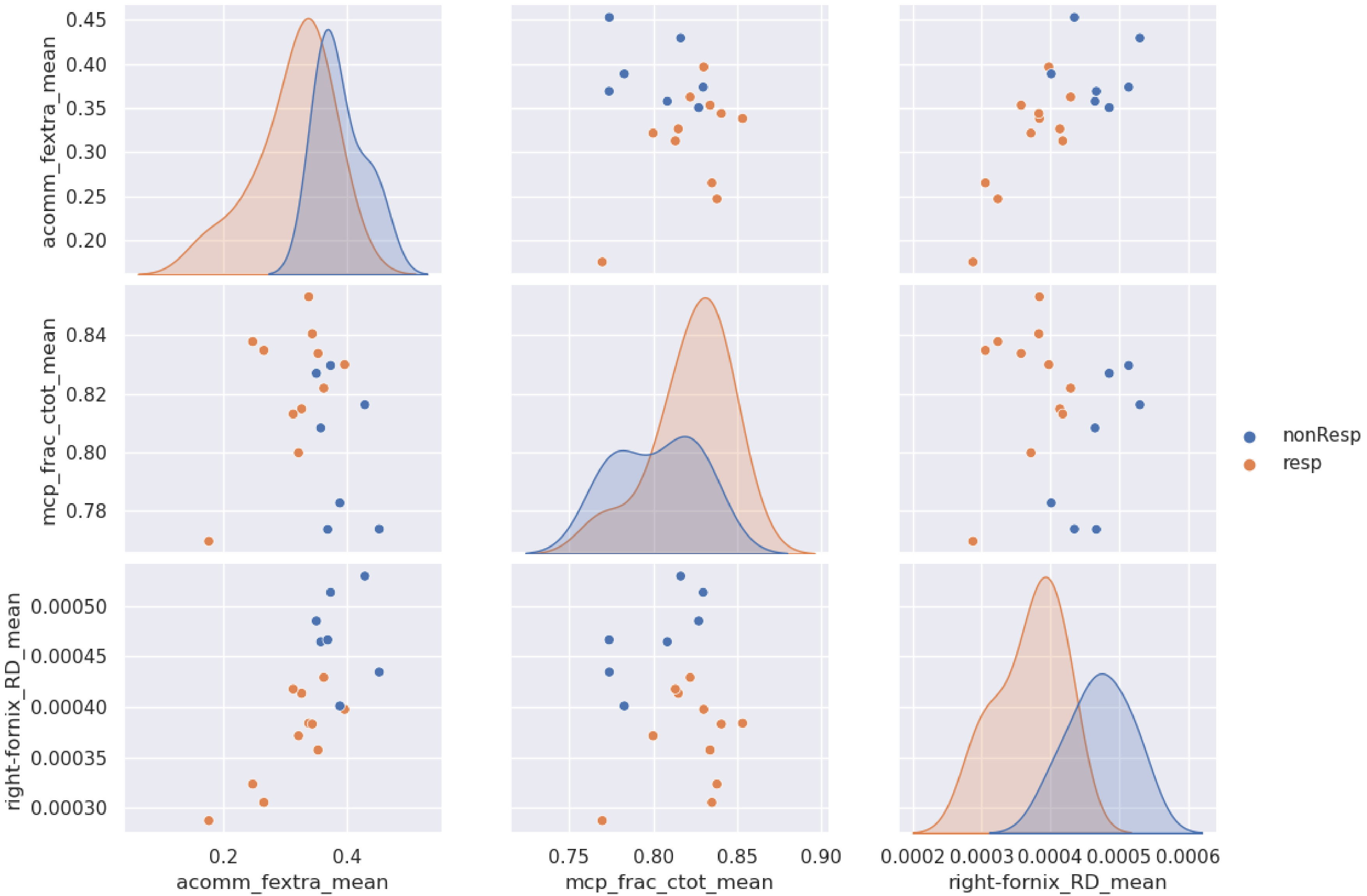


Results: Microstructural Features

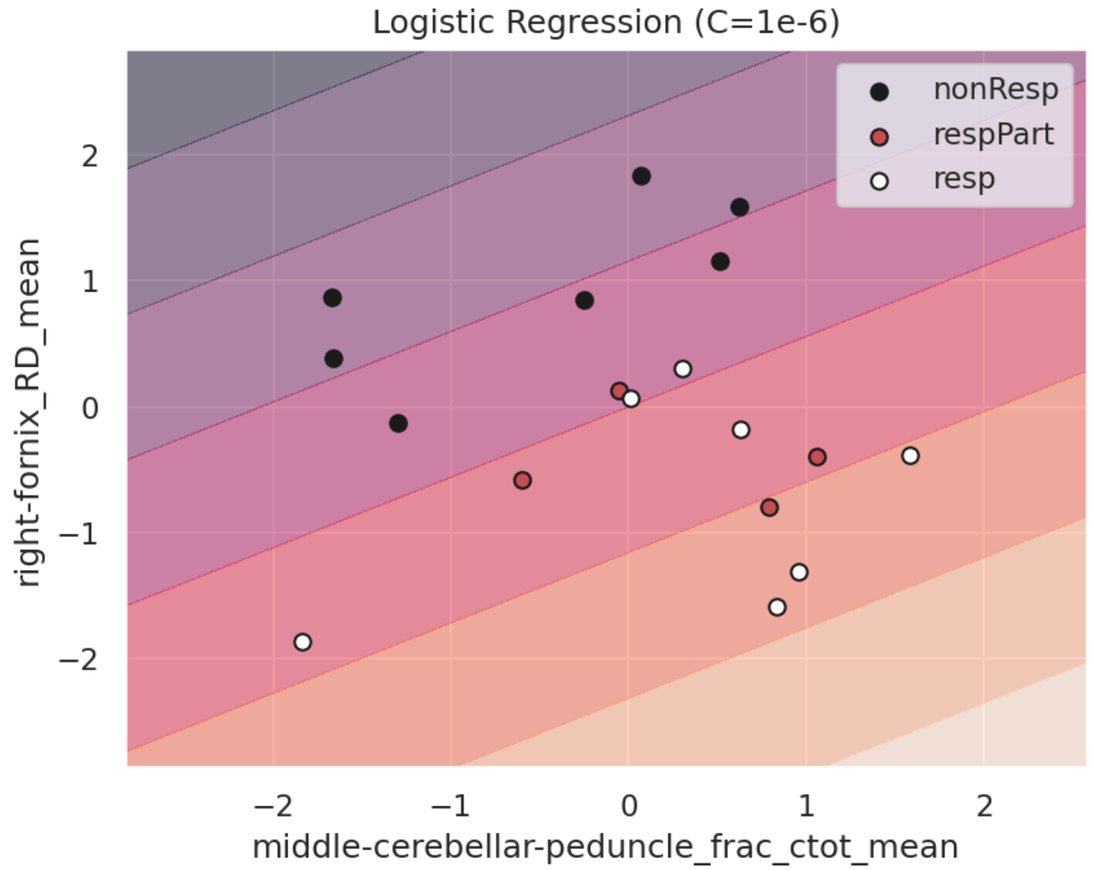
Middle Longitudinal Fasciculus and Optic Radiation

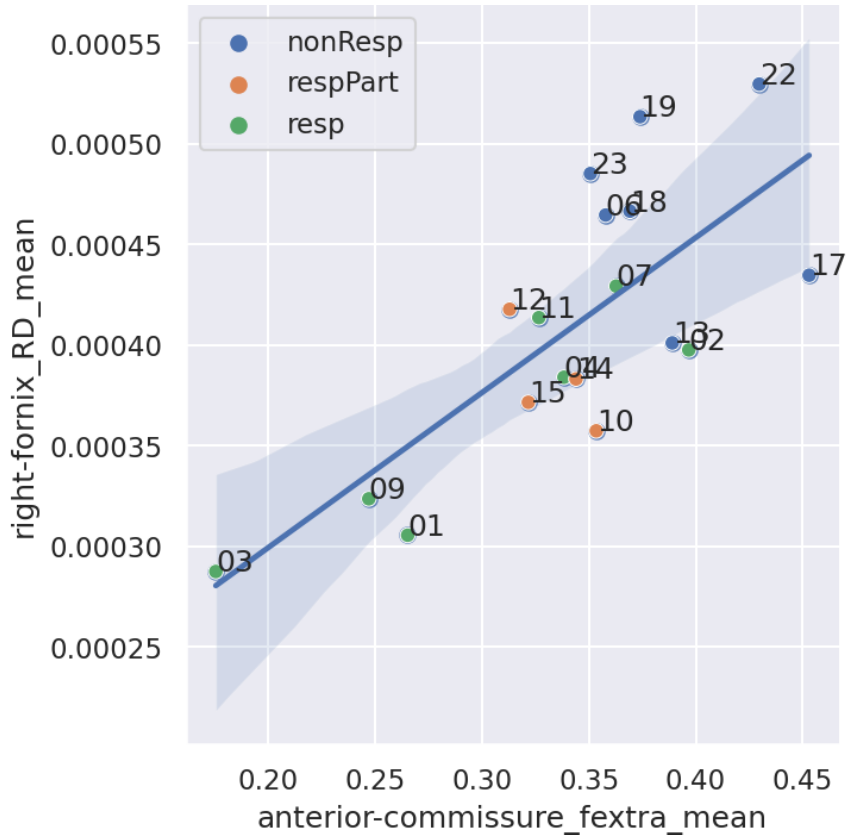


Results: Feature Selection



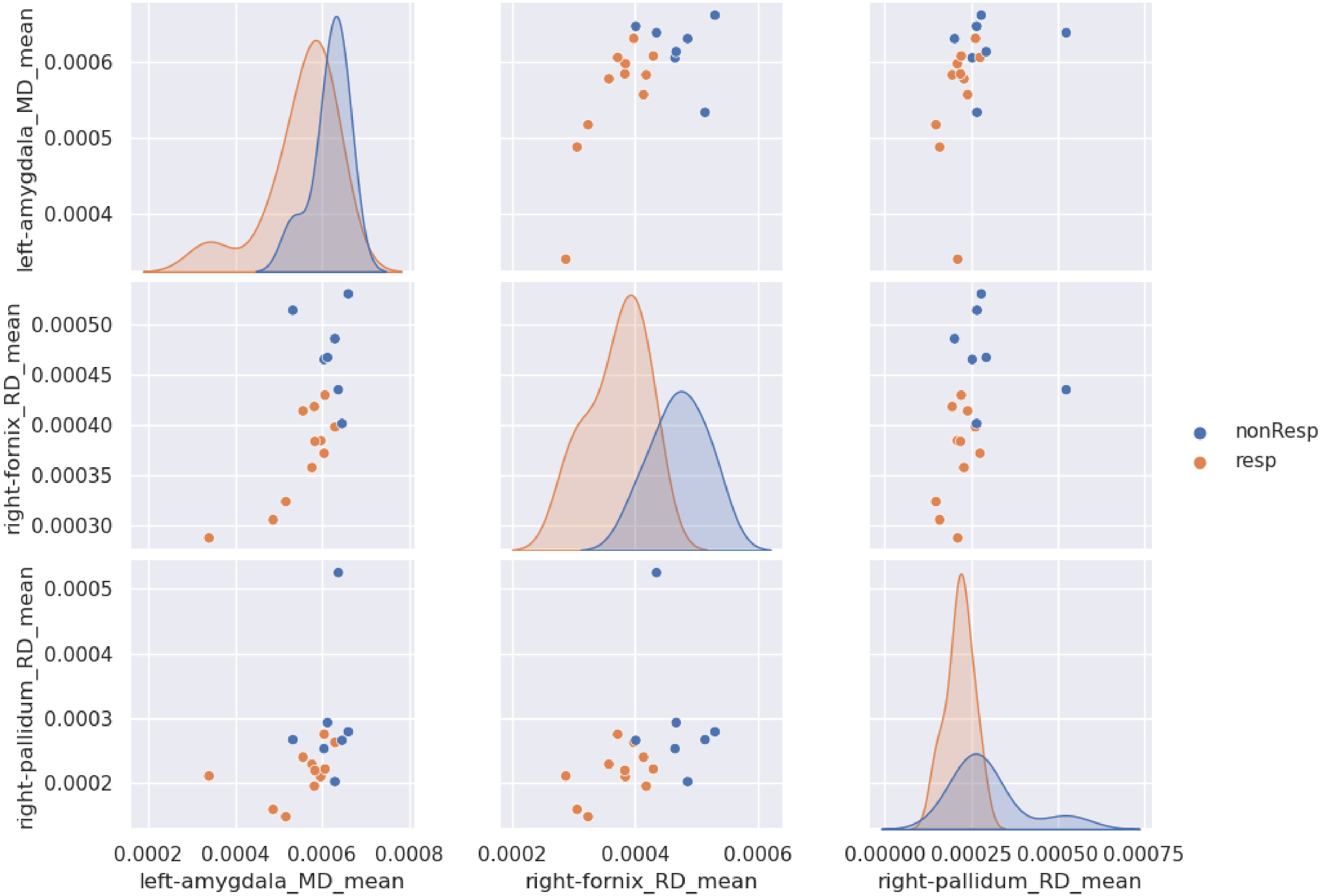
Results: Feature Selection





Stratified shuffle split cross-validation:
AUC=1, F1-score=0.857, Accuracy = 0.833

Results: Feature Selection



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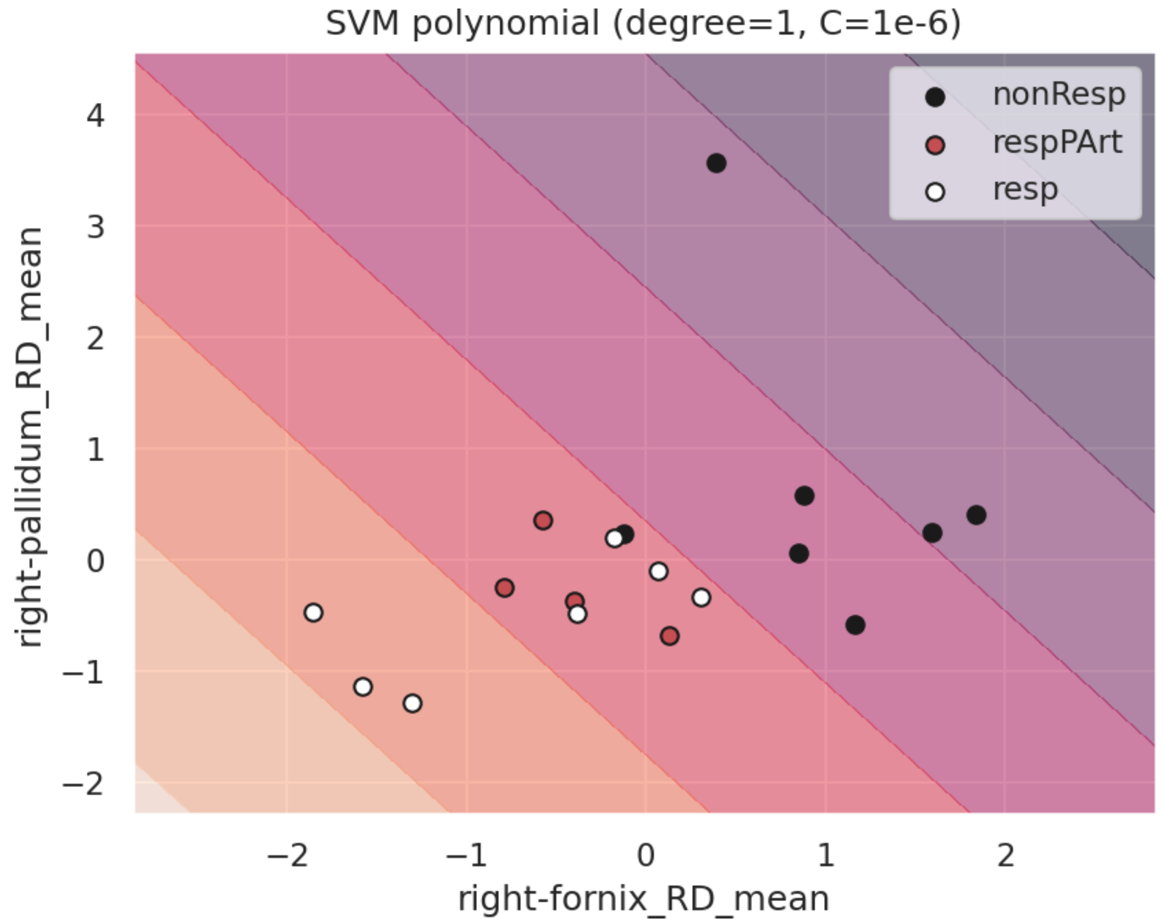
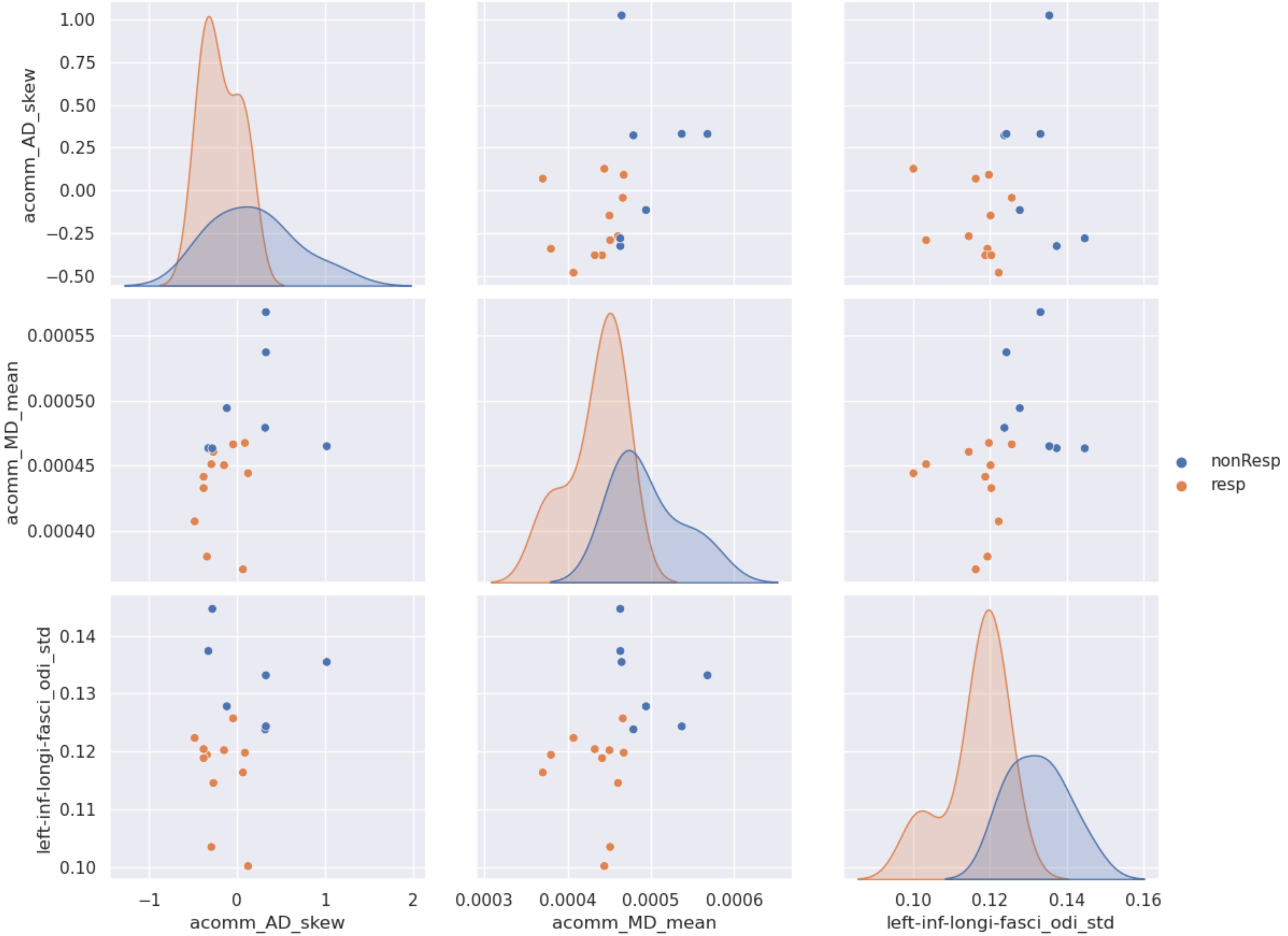
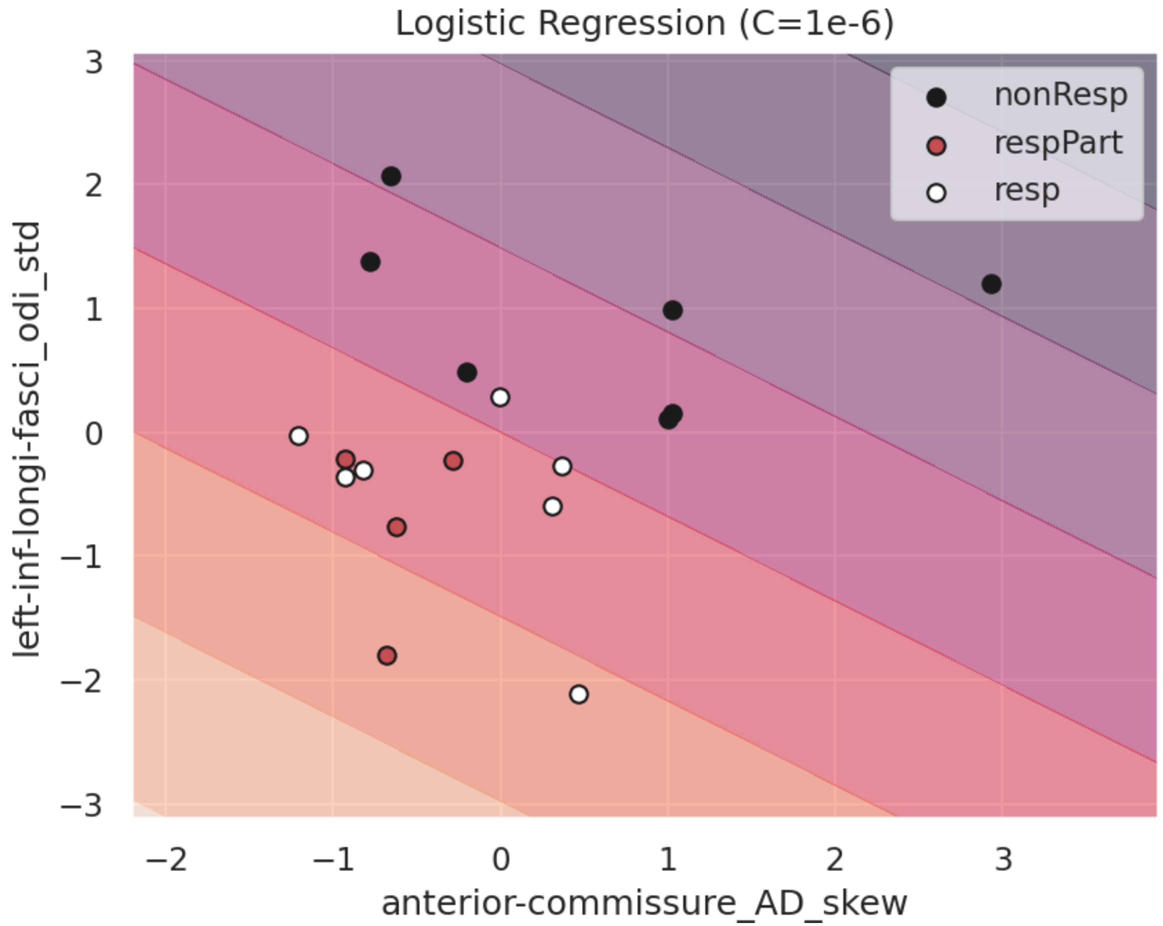


Stratified shuffle split cross-validation:
AUC=0.996, F1-score=0.854, Accuracy = 0.829

Results: Feature Selection



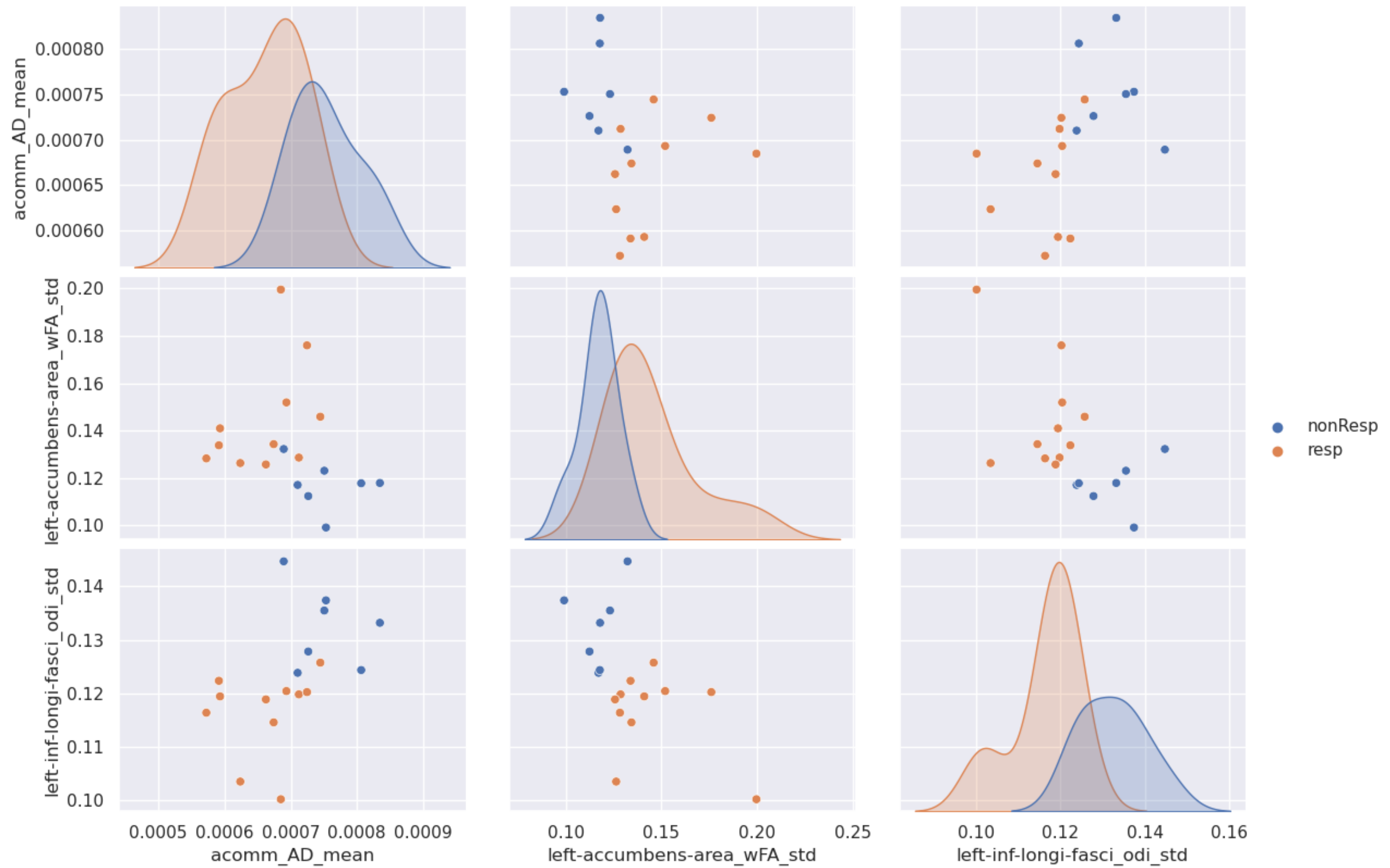
Results: Feature Selection



Stratified shuffle split cross-validation:

AUC=1, F1-score=0.857, Accuracy = 0.833

Results: Feature Selection



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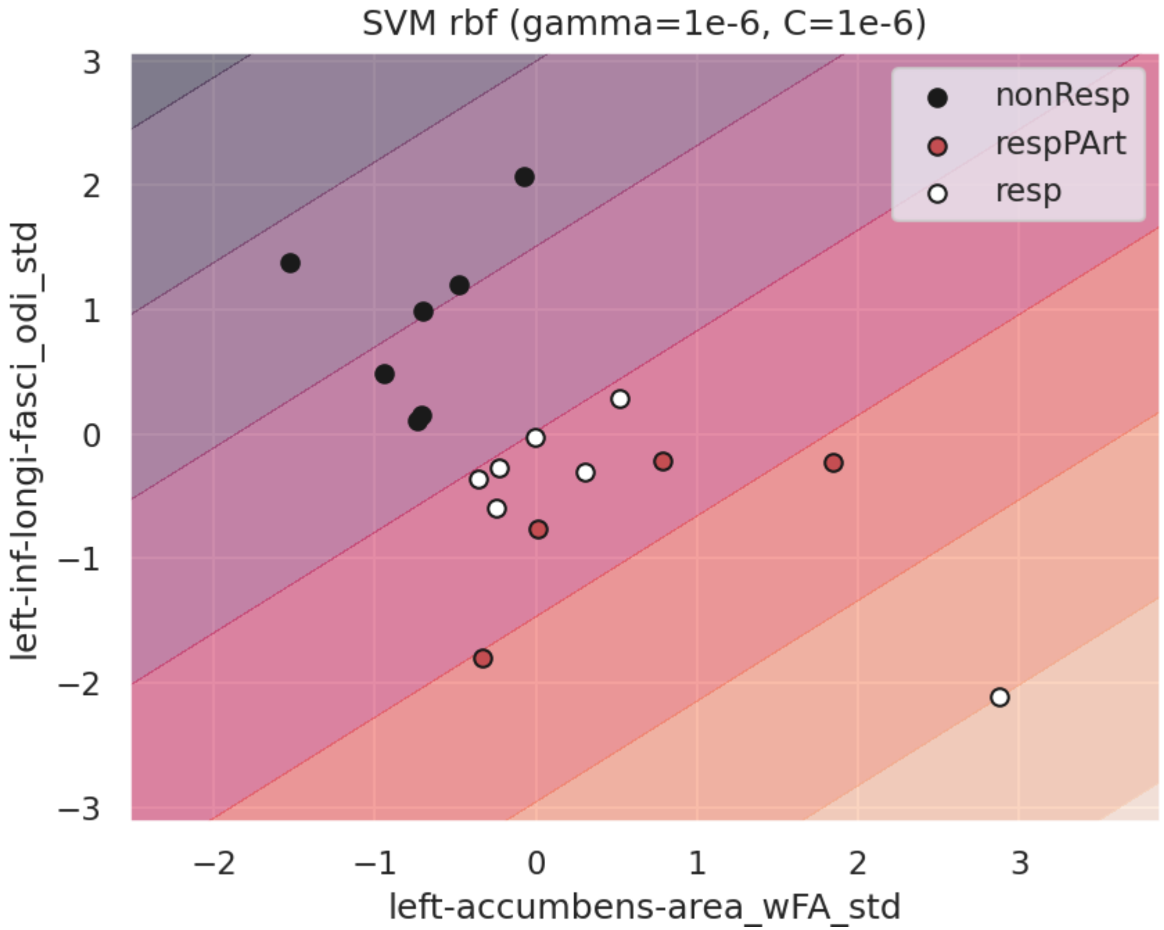

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Discussion: Univariate Analysis

Differences between responders and non-responders were found in the expected tract selected from the literature.

In this study with the explained method the DTI and NODDI models had a greater discriminatory capability than DIAMOND and MF.

In thalamocortical radiations was observed a higher integrity on the left side compared to the right side that may reflect the neuroplasticity of the therapy. However, this hypothesis must be proved by longitudinal studies.

Differently from the results of *Mithani* no differences in FA were found between responders and non-responders.
It is possible that this difference is due to the different method of metric acquisition.

Discussion: Multivariate Analysis

Based on SFS fornix and anterior commissure have a great potential to predict the treatment response in patients with drug-resistant epilepsy.

The classification models built in the present study seems to be robust since an accurate classification was achieved with a lower number of patients.

Similar result have been found in the Mithani's study where they retrieved an estimation of the classification accuracy of 0.895 (AUC = 0.93).

Limitations

Some limitations are present in this study:

- Sample size
- Registration of patients with brain lesions
- Tractography

Future Perspectives

Some limitations are present in this study:

- Healthy control inclusion
- Longitudinal studies
- Metric evolution along the path
- Median of the distribution

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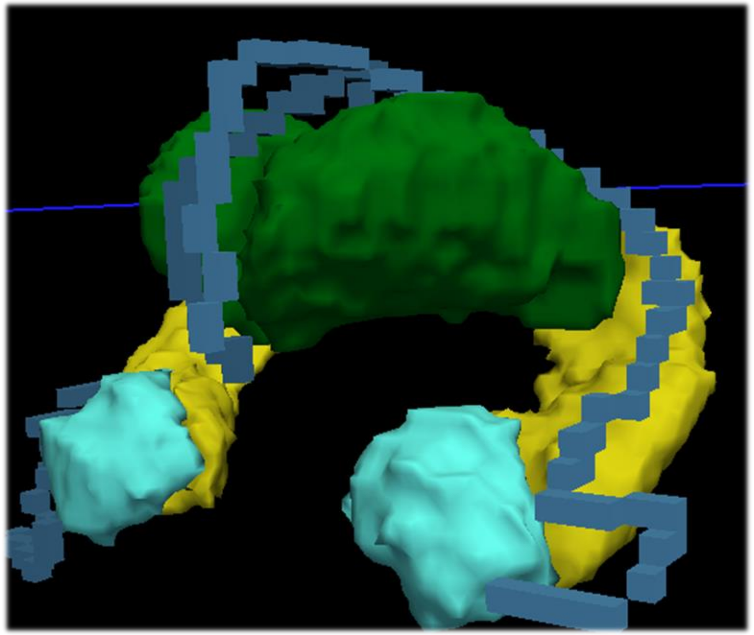

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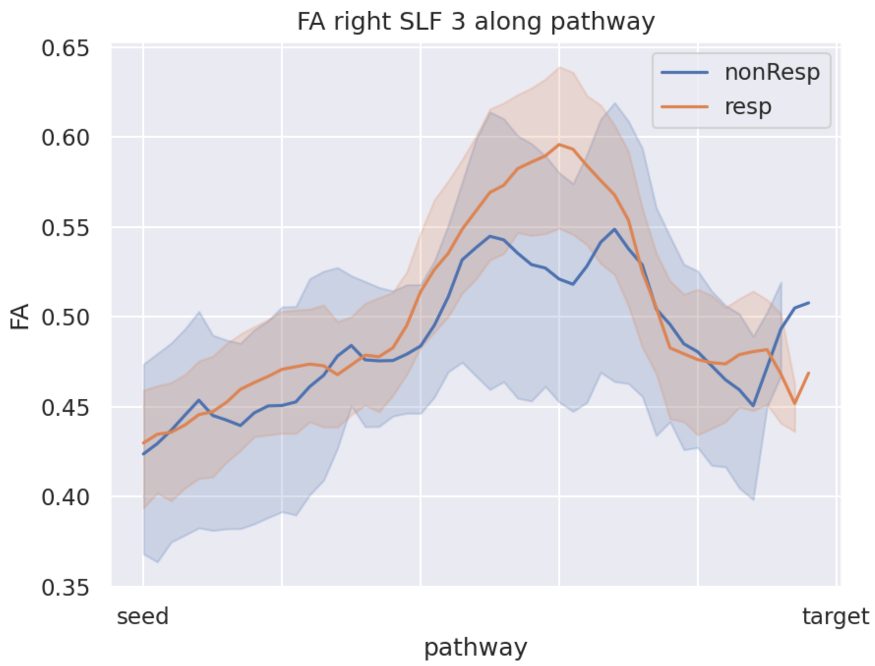

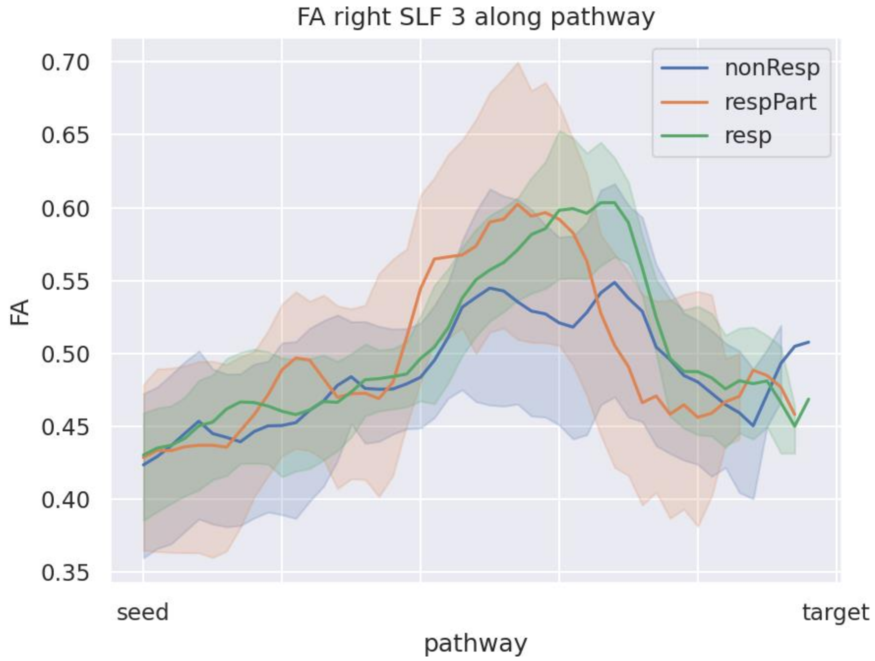

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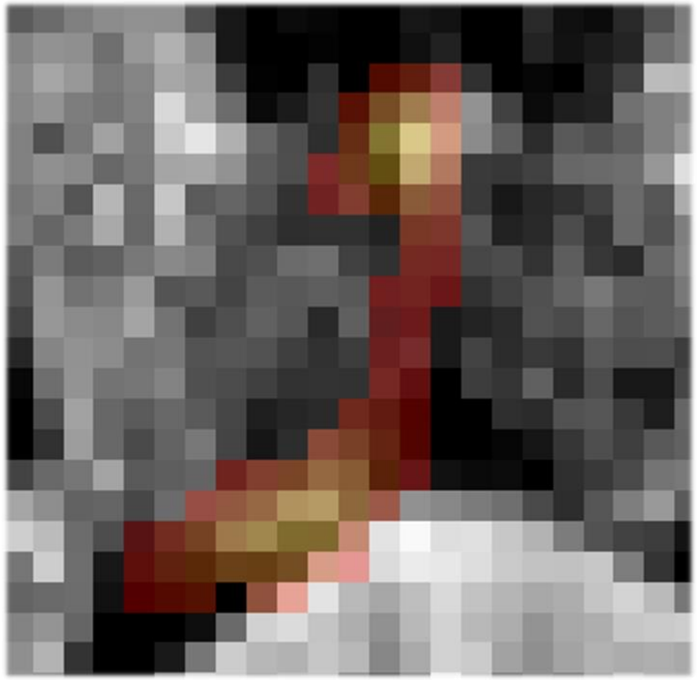

Conclusion

This study was one on of the first that used NODDI, DIAMOND and MF to find biomarkers in drug-resistant epilepsy patients with VNS.

We showed that microstructural connections together with Machine Learning may play a key role to classify responders to Vagus Nerve Stimulation and to find biomarkers.

These results can guide personalized VNS treatment adjustments or reducing the number of unnecessary VNS implantations.