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Classifying cognitively healthy subjects from mild cognitive impaired and Alzheimer's disease patients using Tau-PET: the role of spatial resolution and PET pre-processing

Introduction

- **Spatial distribution** of phosphorylated Tau [1] is a fundamental hallmark of **Alzheimer's Disease** (AD). PET with [18F]-AV-1451 (Tau-PET) probes in-vivo such distribution.
- For motion-robustness and comparability across imaging protocols, Tau-PET investigated over composite regions, for example: Braak stages [1].
- Beyond **Braak composites**, regional Tau-PET uptake **might locally better differentiate** Cognitively Normal (CN), Mild Cognitive Impaired (MCI) and AD.
- **Role of pre-processing** on **group classification performances** currently unclear.

AIMs

1) Compare classifiers trained on Tau-PET SUVR estimates **over two scales**:
- low-resolution Braak composites [1]
- high-resolution whole-brain segmentations (FreeSurfer [2] and LEAP [3])

2) Assess role of **PET pre-processing on classification reproducibility**

KEYWORDS: Tau-PET, Alzheimer's disease, classification, reproducibility

Results

1 - Classification performances: low-resolution Tau-SUVR

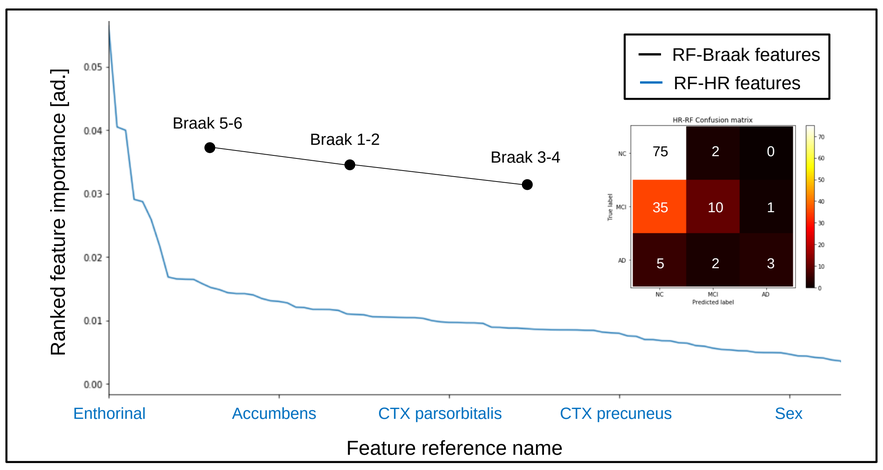
- RF-Braak → statistically significant performances on independent test set: accuracy/recall/precision/F1 (A/R/P/F1) of 0.63/0.63/0.51/0.51.
- Ranking features by importance, SUVR over Braak 5-6 was ranked most discriminative, followed closely by Braak 1-2.
- Confusion matrix revealed high misclassification rate between CN and MCI.

Model	RF-Braak	RF-HR		
Pre-processing	ADNI - FreeSurfer			IXICO - LEAP
Spatial scale	Braak (3 ROIs)	FS (94 ROIs)		LEAP (94 ROIs)
Dataset	Modelling set (validation subset)		Test set	
Accuracy	63%	70%	65%	65%
Recall	63%	70%	65%	65%
Precision	51%	71%	62%	62%

Classification performances summary of random forest models from SUVR across Braak composites (RF-Braak) or higher resolution features (RF-HR) from ADNI (FS-based) or in-house (LEAP atlas matched to FS) pre-processing.

2 - Classification performances: high-resolution Tau-SUVR

- RF-HR → superior group discrimination with significant A/R/P/F1 of 0.70/0.70/0.71/0.66 and similar misclassification rate between NC and MCI to RF-Braak model
- Relevant imaging regions (ranked features): amygdala, hippocampus, entorhinal, parahippocampal, inferior-temporal, insular, frontal and temporal poles, fusiform and lingual cortices, to note also relevant Braak sub-regions.



Feature importance ranking based on random forest models (black trace for RF-Braak; blue trace for RF-HR across ADNI-FS data) and associated confusion matrix.

3 - Classification reproducibility: high-resolution Tau-SUVR

- RF-HR model had similar performance in test and validation sets considering SUVR features from ADNI (FS regions): A/R/P/F1 of 0.65/0.65/0.62/0.62.
- RF-HR exhibited similar performances when classifying test subjects based on feature set obtained from in-house pre-processing (LEAP matched to FS for consistency) with A/R/P/F1 of 0.65/0.65/0.62/0.61

References

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Methodology

Data source ADNI (http://adni.loni.ucla.edu)

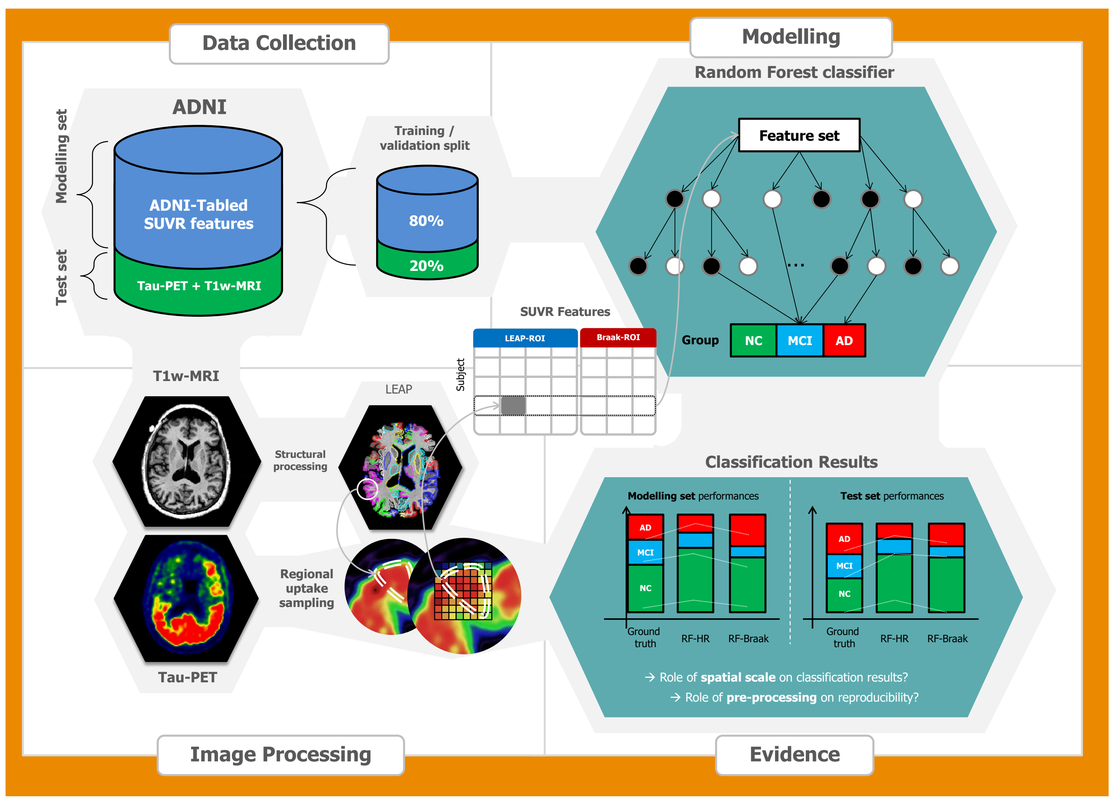
- 610 (380 CN, 173 MCI, 57 AD) Tau-PET datasets: SUVR estimates across 94 FreeSurfer (FS) [4] regions and 3 Braak composites (1+2, 3+4, 5+6)
  - Reference region = cerebellum cortex [5]
- **modelling set**: SUVR of 547 subjects used as feature set for classification experiments
- **test set**: Tau-PET/T1w-MRI images of 63 randomly sampled subjects (35 CN, 11 MCI, 17 AD) simulated an independently acquired study cohort

Test-set image pre-processing

LEAP segmentations of T1w-MRI was registered to native Tau-PET motion-corrected. Regional SUVR was then obtained in 142 LEAP-derived regions of interest (ROI), subsequently spatially mapped over corresponding FS ROIs.

Classification setup

- Modelling set randomly split into training / validation sets: 80% / 20%
- Two **3-class random forests** (20 estimators, 5 samples/leaf min, log2 feature limit) were trained using **SUVR features** across:
  1) low-resolution Braak composites → **RF-Braak model**
  2) high-resolution FS regions → **RF-HR model**
  (*) both included age, sex and education.
- Performances of random forests trained **on the modelling set** (i.e. RF-Braak and RF-HR) were assessed over the **independently processed test-set**:
  → reproducibility with different processing of Tau-PET based classification



METHODS STRUCTURE AND COMPONENTS

Conclusions

- Tau-PET ([18-F]-AV-1451) can **discriminate NC/MCI/AD** offering classification performances **robust to pre-processing differences**.
- SUVR across **Braak composites was less discriminative for MCI and HC than SUVR features from whole-brain segmentations** (high-resolution) even if top-rank features were nonetheless part of such composites, suggesting their aggregation might mask relevant in-vivo Tau-PET patterns.
- The use of a **different Tau-PET pre-processing (IXICO-LEAP) than the used for the training set (ADNI-FS)**, **did not impair the classification** performances on a random independent test set.
- Pre-processing differences here included a different atlas and PET motion-correction/smoothing/resampling steps designed for best Tau-PET sensitivity.

Significance: these results suggest the **feasibility of using classification models trained on comparable datasets to support cross-sectional stratification** over novel Tau-PET studies and trials.