Improved separation of Alzheimer's disease and related disorders using dual-point amyloid-PET

F. Segovia[1], J. M. Górriz[1], J. Ramírez[1], D. Castillo-Barnes[1], F.J. Martinez-Murcia[1], D. Salas-Gonzalez[1], R. Sanchez-Vaño[2], P. Sopena-Novales[2] and M. Gomez-Rio[3]

[1]*Department of Signal Theory, Networking and Communications, University of Granada, Granada, Spain*
[2]*Department of Nuclear Medicine, "9 de Octubre" Hospital, Valencia, Spain*
[3]*Department of Nuclear Medicine, "Virgen de las Nieves" University Hospital, Spain*

INTRODUCTION

- ^{18}F-Florbetaben (FBB) is an amyloid radiotracer that is being increasingly used to assist the diagnosis of Alzheimer's disease (AD).
- Using a Positron Emission Tomography (PET) device, ^{18}F-FBB allows visualizing potential β-amyloid plaques in the brain, which are characteristic hallmarks of AD.
- Internationally accepted criteria for ^{18}F-FBB recommend acquiring PET data during 20 min. and start the acquisition between 45 and 130 min. after injection.
- Recent studies have suggested that early acquisitions (immediately after the radiotracer injection) of ^{18}F-FBB provides information about the downstream neuronal injury, similar to that contained in ^{18}F-FBB-PET images [1,2].

In this work, we analyze the usefulness of using early and standard ^{18}F-FBB-PET images together to develop more accurate Computer Aided Diagnosis (CAD) systems for AD.

- As far as we know this is first time that both, an early and a standard ^{18}F-FBB-PET image are used as a single observation along with a CAD system for AD.

METHODS

- A binary statistical classifier can be seen as a function $f: \mathbb{R}^D \rightarrow \{\pm 1\}$ that is able to predict the class (defined by a binary label) of a new (unseen) D-dimensional pattern. This function is built using training data consisting on a set of N labeled (of known class) D-dimensional patterns:

$$(\mathbf{x}_1, y_1), (\mathbf{x}_2, y_2), \dots, (\mathbf{x}_1, y_1) \in (\mathbb{R}^D \times \pm 1)$$

- Support Vector Machine (SVM) is a statistical classifier that builds the classification function using an hyperplane computed to have the largest distance to the closest training data point of any class. Usually, it is computed as a maximization problem:

$$\text{maximize} \sum_{i=1}^{N} \alpha_i - \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \alpha_i \alpha_j y_i y_j k(\mathbf{x}_i, \mathbf{x}_j)$$

$$\text{subject to} \sum_{i=1}^{N} \alpha_i y_i \, , 0 \leq \alpha_i \leq C, i = 1,2, \dots, N$$

where C stands for a predefined trade-off parameter between model simplicity and classification error, α is the vector of dual variables corresponding to each separation constraint, and $k(\mathbf{x}_i, \mathbf{x}_\mathrm{j})$ is a function $\mathbb{R}^D \times \mathbb{R}^D \rightarrow \mathbb{R}$ known as *kernel*.

- Once the hyperplane is computed, the classifier assigns a group label to each new pattern according to the side of the hyperplane where the pattern is.
- In the classical approach to classify neuroimaging data, each neuroimage is considered as a pattern, $\mathbf{x}_i$, and each voxel as a feature of that pattern:

$$\mathbf{x}_i = \left(x_{i_1}, x_{i_2}, \dots, x_{i_D}\right)$$

- Feature selection and feature extraction techniques can be also applied to reduce the pattern dimensionality.
- We propose to use an early and a standard ^{18}F-FBB-PET image as a single observation in the classification procedure. Two approaches are proposed:
  - Concatenate the voxels from both neuroimages resulting in patterns of $2 \times D$ dimensions:

$$\mathbf{x}_i = \left(x_{i_1}^e, x_{i_2}^e, \dots, x_{i_D}^e, x_{i_1}^s, x_{i_2}^s, \dots, x_{i_D}^s\right)$$

    where $x_{i_j}^e$ and $x_{i_j}^s$ belong to an early and a standard ^{18}F-FBB-PET image respectively.
  - Compute a kernel per each neurorimage and combine resulting kernels as [3]:

$$k(\boldsymbol{x}_i, \boldsymbol{x}_j) = \frac{w_e k_l(\mathbf{x}_i^e, \mathbf{x}_j^e) + w_s k_l(\mathbf{x}_i^s, \mathbf{x}_j^s)}{2}$$

    where $\mathbf{x}_i^e$ and $\mathbf{x}_i^s$ are, respectively, the voxels from early and standard ^{18}F-FBB-PET neuroimages corresponding to patient $\mathbf{x}_i$; w_e and w_s are the weights of each kernel; and $k_l(\mathbf{x}_i, \mathbf{x}_j) = \mathbf{x}_i \mathbf{x}_j^T$.

EXPERIMENTS AND RESULTS

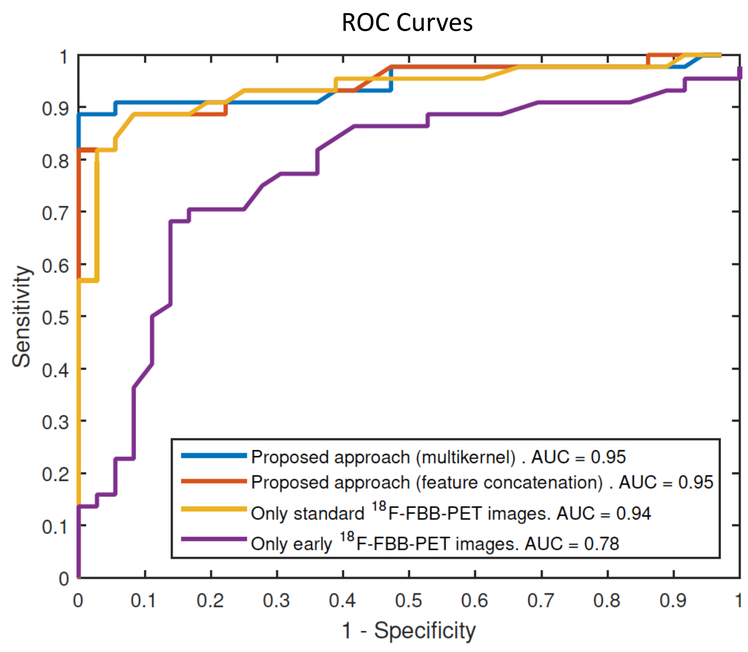
- This study involves data from 80 subjects fulfilling clinical appropriate use criteria for amyloid-PET scan according to international criteria.
- All participants were evaluated by experienced neurologists using standardized clinical and neuropsychological examinations. The evaluation included the acquisition of early and standard ^{18}F-FBB-PET data, i.e. two neuroimages per subject.
- The acquired data were labeled by experienced clinicians after 1 year of clinical monitoring on the basis of changes in the follow-up and results of complementary explorations, including the visual inspection of the neuroimages.

	#	Sex		Age		
		M	F	μ	σ	range
AD patients	44	20	24	63.50	6.59	49-74
Non-AD patients	36	23	13	62.89	8.99	42-79

- All neuroimages were preprocessed following standard procedure:
  - **Spatial registration**. The template matching approach implemented in SPM (version 12) was used.
  - **Intensity normalization**. It was performed by dividing each voxel intensity by the mean intensity of the 0.1% of the voxels with highest intensity.
- A SVM classifier was used to separate patients and controls.
- The performance was estimated by means of a k-fold approach and compared with using only one data modality:

	Accuracy	Sensitivity	Specificity
Proposed approach (two kernels)	92.50 %	86.36 %	100.0 %
Proposed approach (concatenation)	88.75 %	88.64 %	88.89 %
Only standard ^{18}F-FBB-PET data	87.50 %	88.64 %	86.11 %
Only early ^{18}F-FBB-PET data	73.75 %	75.00 %	72.22 %

Proposed approaches achieved higher accuracy rates than previous ones. The greater improvement was obtained with the MKL-based system.



1. F. Segovia et al., «Usefulness of Dual-Point Amyloid PET Scans in Appropriate Use Criteria: A Multicenter Study», Journal of Alzheimer's Disease, vol. 65, n.º 3, pp. 765-779, jul. 2018.
2. S. Daerr et al., «Evaluation of early-phase [18F]-florbetaben PET acquisition in clinical routine cases», Neuroimage Clin, vol. 14, pp. 77-86, oct. 2016.
3. M. Gönen y E. Alpaydın, «Multiple Kernel Learning Algorithms», J. Mach. Learn. Res., vol. 12, pp. 2211–2268, jul. 2011.