# Alzheimer's disease prediction based on machine learning methods applied to multimodal MR features

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## INTRODUCTION

Machine learning (ML) techniques have been of growing interest in the field of medical imaging [1]. The support vector machine (SVM) is a supervised classification ML method: SVM "learns" how to distinguish data that can belong to one of two possible categories (i.e.: healthy subjects, patient), training on examples data (training dataset), than "builds" a prediction model, that can finally be used to assign new data (testing dataset) into one category or the other. The present study focuses on the application of the SVM algorithms for the prediction of Alzheimer's disease (AD) on the basis of measures (features) extracted from structural and diffusions MR scans.

## METHODS

*Subjects and data acquisition:*

We recruited 40 patients diagnosed with probable AD (see TAB.1 for demographic data) according to NINCDS-ADRDA consensus criteria [2], and 28 healthy subjects (HS) (see TAB.1 for demographic data), age and gender matched to the AD group. All subjects underwent a neuropsychological examination and an MRI acquisition at 3.0T. The MRI session included for every subject: (1) T1-weighted (MDEFT) scan (TR=1338ms, TE=2.4ms, Matrix=256x224, n. slices=176, thick=1mm) and (2) Diffusion Weighted (DW) twice-refocused spin echo echo-planar imaging (SE EPI; TR=7s, TE=85ms, b factor=1000s/mm$^2$, isotropic resolution=2.3mm$^3$), collecting seven images with no diffusion weighting (b=0) and 61 images with diffusion gradients applied along 61 non-collinear directions.

*Image analysis and SVM features extraction:*

The MDEFTs were first processed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) to yield maps of GM, WM and CSF volume in native space. No spatial smoothing was performed. Brain tissues volumes (GMvol, WMvol, CSFvol) were calculated for each subject by multiplying the number of voxels in each tissue class (GMmask, WMmask, CSFmask, computed binarizing the relative volume maps with a threshold of 0.5) by the nominal volume of a single voxel. To account for subjects' head size differences, GMvol and WMvol were expressed as percent of the total intracranial volume (TIV=GMvol+WMvol+CSFvol), and yielded the GM fraction (GMf) and WM fraction (WMf; GMf=GMvol/TIV; WMf=WMvol/TIV).

DW images were processed (using FSL, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, and CAMINO, http://cmic.cs.ucl.ac.uk/camino/) to compute the fractional anisotropy (FA), radial diffusivity (RAD) and axial diffusivity (AXD) maps in native space for each subjects. The FA maps were warped to the T1 images (used for the tissues segmentation) and the inverse (non-linear) transformations were applied to GMmasks and WMmasks. This way we could compute for each subject the mean values of FA, RAD, AXD separately in GM and WM, which with GMf and WMf formed the SVM features.

*SVM classifiers:*

The SVM analysis was performed using custom-made Matlab (the MathWorks, Natick, MA, USA) script, exploiting the libSVM library [3]. In particular, we used a non-linear SVM with gaussian (RBF) kernel, to classify (in AD or HS group) features coming from structural (GMf, WMf) and diffusion MR images (mean values of FA, RAD, AXD, separately in GM and WM). Three different SVM classifiers were computed, using three different groups of features: (1) "T1": only structural MR data (GMf, WMf); (2) "DWI": only diffusion MR data (mean values of FA, RAD, AXD in GM and WM); (3) "T1+DWI": structural and diffusion MR data together. For all three SVM classifiers, we tuned the parameters of the SVM model (the soft margin constant, C and the width of the gaussian kernel, γ) through a grid search (using the range from -15 to 25 with step size of 2 for $\log_2 C$ and -25 to 13 with step size of 2 for $\log_2 \gamma$) and Leave-One-Out Cross Validation (LOO-CV). In LOO-CV approach, a single observation from the original sample is used as testing dataset and the remaining observations as training dataset, repeating this until each observation in the sample is used once as testing dataset. The optimized values of C and γ were then used to create the optimized SVM model, whose classification accuracy (i.e., proportion of AD and HS subjects correctly classified, among the whole population), sensitivity (i.e., the proportion of AD patients correctly classified) and specificity (i.e., the proportion of HS correctly classified) were computed.

## RESULTS

The performance of the classifiers built with the different feature groups are summarized in TAB.2. The best accuracy result was obtained using contemporary structural and diffusion features (see "T1+DWI" features group in TAB.2); the "T1+DWI" SVM globally misclassified 5 subjects (3 AD and 2 HS) out of 68 (40 AD and 28 HS). There were little differences in accuracy, sensitivity, and specificity among "T1+DWI" and "T1" SVMs, but the former overcame the latter in the direct comparison of each performance parameter. The "DWI" SVM had the best sensitivity, but a very low specificity and the worst accuracy.

**TAB 1**. Demographic information.

| | **AD** (n=40; 25F/15M) | | | **HS** (n=28; 12F/16M) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | Range | Mean | SD | Range |
| **Age** | 69.5 | 6.5 | 55-79 | 66.4 | 7.0 | 56-81 |
| **MMSE** | 19.1 | 4.3 | 11-28 | 28.8 | 1.6 | 25-30 |

AD = Alzheimer's Disease; HS=Healthy Subjects; MMSE = Mini-Mental State Examination.

**TAB 2**. SVM classification performance for different feature groups.

| **Features (#)** | **ACC** (%) | **SEN** (%) | **SPE** (%) |
|---|---|---|---|
| **T1** (2) | 89.7 | 90.0 | 89.3 |
| **DWI** (6) | 85.3 | 97.5 | 67.9 |
| **T1+DWI** (8) | 92.6 | 92.5 | 92.9 |

ACC = accuracy; SEN = sensitivity; SPE = specificity. T1 features: GMf, WMf. DWI features: mean FA, mean RAD, mean AXD, separately in GM and WM.

## DISCUSSION

In the current study, we investigated the classification between HS and patients with AD, using multimodal (structural and diffusion) MR data as input to SVM classifiers. We found that structural MR features had higher discrimination capability relative to diffusion ones, but the best classification performance was obtained combining them (TAB.2). This finding indicates that, as expected, structural and diffusion MR properties (both in GM and WM) provide complementary information on the dementia status. It should be noticed that we obtained satisfactory classification performance despite the utilization of very few features, considering that it is not uncommon to use hundreds or thousands features to improve the classification performance [4, 5, 6]. Furthermore, the use of a small number of features allowed a faster computation of the SVM classifiers, even with LOO-CV approach. This last characteristic, together with the evidence that the computation of the features we used is nearly completely automatable, make our approach suitable to be adopted into clinical practice. Further work may be directed to (1) use additional image modalities (Magnetization Transfer, Resting State-fMRI) to improve the classification performance and (2) test the ability of the classifier to simultaneously discriminate multiple stages of dementia, including for example an additional group of Mild Cognitive Impaired subjects.

## References

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