Global Disease Index, a novel tool for MTL atrophy assessment.

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Abstract. Hippocampi and medial temporal lobe (MTL) structures are notoriously among the first anatomical districts to be troubled by Alzheimer's Disease (AD). Accurate atrophy quantification for temporal and cortical brain structures is considered a promising marker for prodromal AD, thus the urge upon finding suitable automatic tools to perform voxel-based-morphometry tasks such as anatomical structures segmentation, shapes outlining and features selection.
We propose an original neuroanatomical approach, called "Global Disease Index" (GDI), stemming from the methodology appeared in [1]. It is a profound reworking of that procedure, based on local analysis of 9 MRI regional volumes of interest (VOIs) containing relevant MTL structures. These VOIs are filtered by means of a Random Forest classifier in order to enhance peculiar image features found to be the most significant to discriminate between cognitively normal subjects and Alzheimer's Disease patients. These features are subsequently processed with a Random Forest and a Support Vector Machines classifiers, providing an assessment of MTL atrophy in the form of a classification index.
The procedure proved to be a robust and reliable tool, able to distinguish with fine accuracy CN, AD and MCI. On MICCAI's CADDementia Grand Challenge provided train data, GDI has demonstrated a detection power of 93.5%, 68.9%, 92.6% of AUC for CN, MCI and AD cohorts respectively, supporting the reliability of the overall algorithm.

Keywords: Alzheimer's Disease, MRI, MTL atrophy

Abbreviations: GDI: Global Disease Index, AD: Alzheimer's Disease; CN: Cognitively Normal; MCI: Mild Cognitive Impairment; MCI-conv: MCI converter; MCI-nonconv: MCI non converter; VOI: Volume of Interest; RF: Random Forest; SVM: Support Vector Machines; AUC: Area Under Curve;

* Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (`http://www.loni.ucla.edu/ADNI`). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at `http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Authorship_list.pdf`.

1 Introduction

The past 10 years have seen a growing consensus that the atrophy of medial temporal lobe structures can potentially be crucial to capture early AD onset and disease progression by means of T1-weighted MR images analysis. In particular atrophy of the hippocampus induced by AD may reasonably be a specific biomarker of pathology progression, known that volume loss in hippocampi is strictly connected to increasing impairment in cognitive performances of afflicted the subjects [2]. This fact justifies the need of defining reliable quantification methods to assess changes in MTL morphology. In the case of hippocampal volume, a commonly accepted and clinically validated automatic segmentation procedure would quickly replace traditional time-consuming and rater-dependent manual tracing protocols.

Automatic approaches are introduced, as the one proposed in [3], permitting accurate extraction of desired Volumes of Interest (VOIs) from MRI, on which voxel-based morphometry indicators can be computed.

We present in this work an analysis pipeline build to automatically assess the progression of brain atrophy brought by AD in medial temporal lobe structures.

The technique, named GDI, is based on major improvements of the feature selection and classification procedure seen in [1], to study intensity and textural characteristics of a set selected volumes surrounding MTL structures to discriminate AD and CTRL subjects.

The core of the methodology is the local analysis of 9 MRI regions of interest containing relevant MTL anatomical structures. These VOIs are filtered by means of a Random Forest (RF) classifier in order to select, in the target MRI, image features previously found to be significant to discriminate between CN subjects and AD patients. These voxels are are processed with classifiers (RF plus SVM), providing an index assessing overall MTL atrophy.

2 Materials & Methods

We propose an improvement of the procedure designed in [1]. The procedure is fully automated and needs an average time of 45 minutes to complete a single subject scan analysis, on an average single core computer with 2.27 GHz, 64 bit system. We noticed that GDI analysis speed depends more on computer clock-cycle than on its memory or file system characteristics. The most resource demanding steps in the pipeline are registrations and volumes extractions.

2.1 Subjects

Data used in the preparation of this work consist in a sample of 551 baseline MRI, of just as many subjects, downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database
(`http://www.loni.ucla.edu/ADNI/Data`). Images were acquired all with 1.5 T

scanners, whilst scanners' type can be different and used with different acquisition protocols.

Statistical information on this training cohort is summarized in Table 1.

Table 1. ADNI train sample.

Cohort	Size	Gender	Age
CN	190	95 M, 95 F	76.6 ± 5.5
AD	195	66 M, 79 F	76.6 ± 7.8
MCI	166	71 M, 45 F	75.5 ± 7.4

AD cohort includes 50 MCI subjects who converted to AD after a follow-up of 2 years (MCI-conv), while MCI cohort includes only MCI subjects who retained the same clinical assessment after a follow-up of 2 years (MCI-nonconv). The ground for the decision to merge the MCI-conv into the AD cohort, was to keep the MCI cohort, with only MCI-nonconv, distinct from the AD [6, 7].

The 30 MRI provided by CADDementia organizers are employed to fine tune the procedure free parameters. 13 of these scans come from the EMC: Erasmus MC center (Rotterdam, the Netherlands), 3 scans from the UP: University of Porto - Hospital de São João, and 14 from the VUMC: VU University Medical Center (Amsterdam, the Netherlands).

2.2 MRI analysis

The main steps of GDI workflow are image preprocessing (noise reduction and registration), multiple template-based anatomical structure registration, extracted volumes intensity normalization, features enhancement, and Random Forest plus Support Vector Machines features classification.

Each target image is processed with a pyramid noise-filtering algorithm [4] to promote image uniformity across sites and machines. The difference with respect to previous paper is that the 3 thresholds N_t necessary to extend to 3D the algorithm are no longer automatically calibrated for every image and every direction based on the Structural Similarity Index (SSI) curve, but are replaced with a single fixed value corresponding to the mean value of all N_t calculated on training data in the original procedure. The reason behind this choice is that dynamic threshold denoise was found to much invasive and image dependent. A fixed threshold sensibly reduces running time of denoising module.

De-noised scans are then registered and re-sampled onto the Montreal Neurological Institute (MNI) ICBM152 reference, with a $1mm^3$ isotropic grid [5]. The 3-fold registration process of the ancestor paper has been substituted with a faster, single registration process implemented with Insight Toolkit (ITK, `www.itk.org/`). Each incoming image is subjected to a rigid registration with

7 degree of freedom (similarity registration) and to an affine registration. This simplified and faster workflow has comparable performances to the original one.

Once preprocessed in this way, each MRI is sampled with 9 VOIs with different dimensions placed around pertinent biological entities in MTL and cortex (refer to Figure 1), to reduce analysis burden. This VOIs are chosen to include those temporal lobe structures that are known to be affected in early AD, such as the entorhinal, perirhinal cortex, hippocampus and parahippocampal gyri, irrespective of normal inter- and intra-individual variability. Two additional VOIs are chosen as control volumes, in regions known to be relatively spared in early AD.

This extraction operation, producing parallelepiped-shaped volumes containing the desired anatomical structures, is carried on, in order to preserve accurate anatomical correspondence, by means of a rigid registration using references; i.e. a registration of several predefined VOIs onto the subject MNI-normalized brain. There are at least 8-10 references for each contra-lateral target object.

These template VOIs are designed to capture the morphological differences among subjects showing varying degrees of neurodegeneration, ranging from healthy elderly to severe AD. Details on the generation of VOI references can be found in [3].

VOI extraction step has the advantage of providing a reliable method to circumscribe noticeable structures and nearby tissues with reasonably high accuracy and reproducibility among subjects and machineries.

The intensity normalization operation is now applied on registered boxes. Mean values of CSF/Gray Matter/White Matter within the target VOI are obtained with k-means cluster analysis [8].

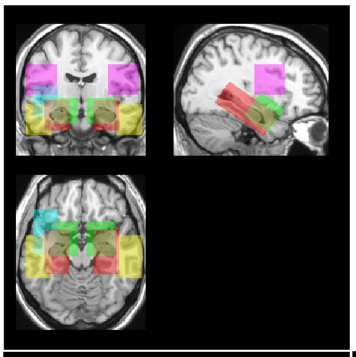
New intensity values are obtained by non-linear matching of these 3 values to the 3 mean segmented cluster values found for a $n = 50 \times 120 \times 50$ voxel region extracted around the corpus callosum of the MNI template. This mapping is extended to intermediate intensities with a smooth piece-wise polynomial curve.

All 9 normalized VOIs from each MRI are now filtered to highlight a reduced set of relevant voxels.

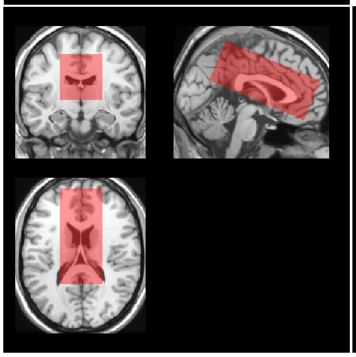
We used 18 different filters (Gaussian mean, standard deviation, range, entropy and Mexican-hat filters calculated on different voxel neighbourhoods), therefore the feature set for each subject under analysis consists of the ensemble of all voxels of the filtered VOIs extracted from its MRI. These features are subsequently pruned by means of RF, keeping the 85% most significant ones in terms of training set CN vs AD distinction [1].

On the output restricted collection of MRI features a Random Forest and a Support Vector Machines classifiers are built.

GDI value is then calculated combining the outcome of the 2 classifiers: a weighted mean of the two values is computed, considering the GDI intervals in which every classifier is more reliable.



	VOI n.	Main anatomical structures
[a]	1	Hippocampus, enthorinal cortex (right)
	2	Hippocampus, enthorinal cortex (left)
	3	Amigdala (right)
	4	Amigdala (left)
	5	Middle and inf. temp. gyrus (right)
	6	Middle and inf. temp. gyrus (left)
	7	Insula - Sup. temporal gyrus (left)
[b]	8	Rolandic (right)
	9	Rolandic (left)



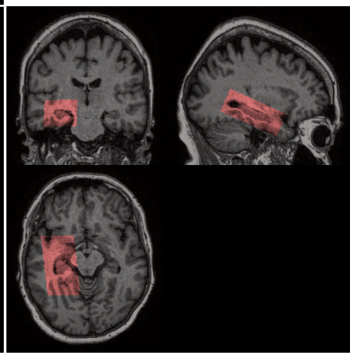


Fig. 1. (*Above Left*) VOI size and positioning displayed on the MNI reference image. VOI n. 1,2: red; VOI n. 3,4: green; VOI n. 5,6: yellow; VOI n. 7: cyan; VOI n. 8,9: magenta. (*Above Right*) Main gray matter structures captured in the VOIs; [a] potentially significant regions; [b] control regions. (*Below Left*) Intensity normalization VOI size and positioning displayed on the MNI reference image. Such a region serves as basis for the histogram matching procedure, following the segmentation into CSF/GM/WM. (*Below Right*) Example of hippocampal VOI registration on a test subject.

2.3 Classification

Each subject is given a membership probability to each group (CN, MCI and AD). Probability Distributions, depicted in Figure 2, are generated with the GDI values coming from the classification of the 30 CADDementia train images.

The GDI index of a new image is evaluated as member of all PDF curves, producing 3 probability values in CN, MCI and AD distributions.

These values are normalized to one and the final class is assigned to the subject with a winner-takes-all scheme (the class with the greatest probability is the winning one).

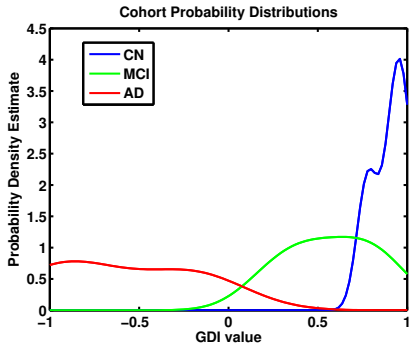


Fig. 2. Probability density estimates calculated from the 30 CADDementia training images. The restricted number of samples is the reason why curves show some bumps. The integral of each curve equals 1.

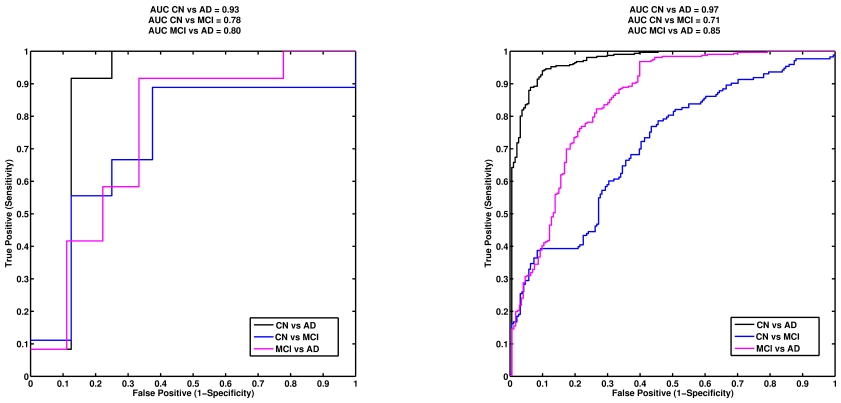


Fig. 3. Performances for the distinction of CN from AD (black curve), CN from MCI (blue curve) and MCI from AD (magenta curve) on CADDementia training sample (*Left*) and on ADNI sample data (*Right*).

3 Results

GDI index discriminates, in Leave-20-Out cross-validation, CN from AD, CN from MCI and MCI from with AUC values of 0.97 (sensitivity = 0.94 @ specificity = 0.90), 0.71 (sensitivity = 0.77 @ specificity = 0.78) and 0.85 (sensitivity 0.86 @ specificity = 0.64).

The classification results on CADDemetia train dataset stands at AUC values of 0.93 for CN vs AD discrimination (sensitivity = 0.92 @ specificity = 0.88), AUC = 0.78 for CN vs MCI (sensitivity = 0.92 @ specificity = 0.67) and 0.8 for MCI vs AD distinction (sensitivity = 0.89 @ specificity = 0.62).

This outcomes can also be seen in terms of One-versus-All classes detection. In this case CN subjects are identified with AUC of 0.935, MCI with AUC of 0.689 and AD with AUC of 0.926. The accuracy of the CN/MCI/AD classification on the CADDementia training data is 0.733. Performances are represented in Figures 3 and 4.

On the other hand blind classification of the test population delivers 146 subjects as cognitively normal, their GDI index centered on a mean value of 0.85 with a standard deviation of ± 0.06, 125 as mild cognitive impairment (GDI in 0.51 ± 0.16) and 83 as Alzheimer's Disease (GDI in -0.31 ± 0.29).

Classification index strictly depends on the goodness of the registration outcome. At the end of the automatic process we visually checked the registered images finding that a very little percentage of them has been poorly registered. This fact had not prevented the algorithm to proceed, so that we have no missing data in our analysis. However we reckon that this fact produces an uncertainty on our results which can be quantified: 3% on ADNI and 6 subjects in 354 on the CADD test sample.

4 Discussion

GDI procedure needs an average cpu-time of 45 minutes to process a 1.5T MRI and provides an index that is an assessment of MTL atrophy progression. GDI index reliability strongly depends on image registration process, and we noticed that approximately 3% of processed image is not properly registered. Nevertheless this index has been used to detect CN, MCI and AD cohorts in CADDementia train dataset with fine accuracy (93.5%, 68.9%, 92.6% respectively).

Incidentally, we have developed a filter testing registration accuracy by means of simple correlation coefficient with the reference template, in a way that we've been able, during training phase with ADNI data, to reject little correlated registration outcomes or to re-register them with more suitable parameters.

For what regards classification results, the not so optimal performances on CN vs MCI distinction can be explained looking at the consistent overlap of their probability distributions. On the contrary, MCI and AD present a delicate area of overlap (around 0.2), while CN and AD populations are almost completely separated in terms of GDI index (Figure 2).

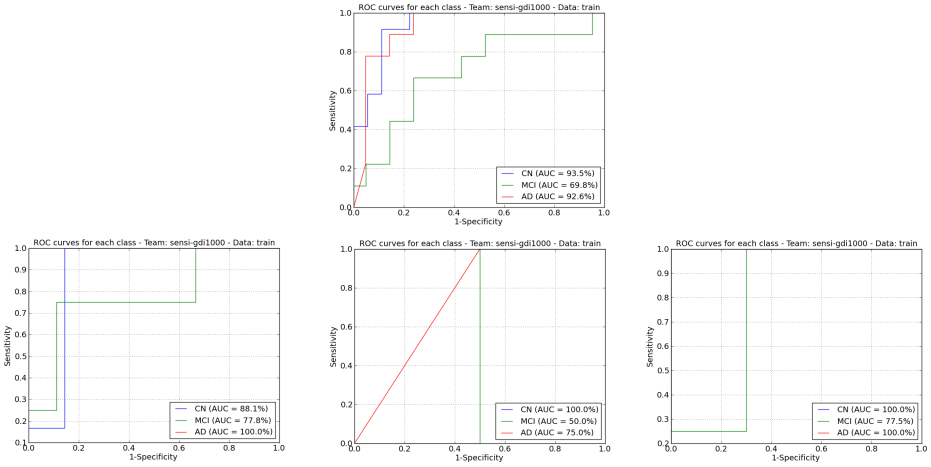


Fig. 4. (*Above*) ROC curves for the detection of CN, MCI and AD for all training data of CADDementia challenge together, and (*Below*) considered separately for each of the three provided database subsets EMC, UP, VUMC (see 2.1).

5 Conclusions

In the current study we have shown an automatic system providing an index working as an objective measure of hippocampal and temporal lobe atrophy and its performance on the training and test data available in CADDementia.

The algorithm characteristics - such a speed and required computational resources - make it suitable to work on grid environment or to be provided as remote web-service.

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