Predictive and Populational Model for Alzheimer's Disease Using Structural Neuroimaging

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Abstract—**This paper aims populational modeling of volumetric degeneration of the gray matter due to Alzheimer's disease, to establish the parameters of degeneration, and to contrast the state of an individual with respect to that model. In this way, you can get an early diagnosis of the disease.**

We have used 2100 structural magnetic resonance images (sMRI), classified by sex (1097 M/1003 F), and corresponding to healthy people (C, Controls) and with Dementia (AD, Alzheimer's Disease), between 18 and 96 años (M-C: 59.44±24, F-C: 60.75±22.79/ M-AD: 75.35±7.07, F-C: 74.23±8.02), from public domain databases.

The SMRI processing methodology uses filtering, segmentation algorithms, and the calculation of parameters such as cortical thickness or volume. Furthermore, registration was performed on each subject with a standard template and a 116 anatomical structures atlas in which the above parameters are calculated.

It was possible to establish which structural changes the brain undergoes when affected by Alzheimer's disease, according to criteria of loss of volume or gray matter thickness, relative to healthy subjects: paracentral lobe, angular gyrus, calcarine sulcus ($p<0.001$), among others. some rules Have also been developed for classifying (error <9%) a given subject as normal or with Alzheimer with a given probability.

We generated a model of Alzheimer's disease, using statistical techniques and imaging processing. This study shows the brain areas that atrophy faster with the disease, and in what sequence they do.

Keywords—**Mild Cognitive Impairment, Early Diagnosis, Neuroimage, Computational Intelligence, Validation.**

I. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease, progressive and irreversible, characterized by cognitive impairment, whose onset occurs in adulthood, especially in people over 65 years. In developed countries it is considered the most common cause of neurodegenerative dementia. Among the population over 65 years, it is the second leading cause of death and the leading cause of dependency. The AD has already become a public health problem that will worsen in the coming decades.

This disease may begin to develop up to ten years before clinical symptoms start. Current diagnostic criteria for the AD require cognitive deficits and dementia are relevant, ie when the diagnosis is made, there are already a large number of affected brain areas and a major neuropathological damage.

A high percentage of cases are diagnosed and treated when the AD is in mild and moderate stages of dementia. Currently there are effective treatments for both mild stage dementia and moderate, but the results indicate that once diagnosed it is too late to recover lost cognitive functions or control its progression [1,2,3].

In recent years there have been a significant number of articles aimed at the early detection of AD, before the onset of dementia and be too late to reverse the course of this disease. Thus, currently the major research lines are aimed at the identification of biomarkers in cerebrospinal fluid (CSF) and neuroimaging.

With regard to the search for chemical biomarkers present in CSF several studies have shown a correlation between AD and AB42 concentration, total tau protein, etc. All these markers involve an important advance in this area, but its invasive nature could be an issue of some importance [4].

But it is the Neuroimaging which, thanks to advances in technology, can provide reliable information on the structure and brain function.

The Magnetic Resonance Imaging (MRI) provides structural and functional information. A major research activity, ultimately being able to speak of "Cortical Thickness" or coactivation patterns, Difussion Tensor Imaging, etc.. Reasonable costs, its complete safety for the patient, scientific and technical improvements continued, and its wide dissemination in hospitals make it, from our point of view, a great candidate for use in the determination of the phases of early AD.

In addition, Information Technology and Telecommunications (ICT) provide a wide range of possibilities, including the possibility of tools and techniques that automatically provide objective data on the structural and functional state of the brain of the subject or subjects under study. From these data, one can obtain, also automatically, a pattern of degeneration in the case of AD and early AD.

In this context, the most appropriate tools for generating computer models (automatic) are those included within the so-called Computational Intelligence and Data Mining.

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These techniques are designed to extract information and knowledge from raw data. The information generated from the data (results of a neuroimaging study, for example) can be easily interpreted by a human expert as a causal model formed by logical rules. These rules express the cause and effect relationships between the different variables of the system and the study's conclusion. For example, a study by MRI provides a number of parameters measured in the image, such as cortical thickness and volume of internal structures of the brain. The computer model can generate rules that associate different values of these parameters with the subject's mental state, indicating so those brain structures associated with that state of mind.

The objectives of this work are summarized in:

a) Propose a robust methodology imaging processing, so that the selected algorithms can commit the slightest error, and thus get ensure statistical validity of the results of neuroimaging studies.
b) Develop a population model of the structural changes that occur in the progression of Alzheimer's disease from its initial stages and mild cognitive dementia to the most advanced form of the disease.
c) Develop and implement an automated system for the early detection of early AD, by processing neuroimaging, and building automated tools and objective techniques based on Artificial Intelligence and Data Mining.
d) Validate the results of the proposed model, determining their sensitivity, specificity and predictive value.

II. MATERIALS AND METHODS

The MRI scans structural used in this study were obtained from databases with public access, such as ADNI [5](Alzheimer's Disease Neuroimaging Initiative) and OASIS [6] (Open Access Series of Imaging Studies), corresponding to normal subjects and AD in various stages.

The first one corresponds to an initiative of the LONI (Laboratory of Neuro Imaging) at the University of California at Los Angeles (UCLA). Its purpose is to collect and make accessible to all researchers who wish a number of brain imaging from both normal subjects and subjects with AD in different stages of evolution.

On the other hand, OASIS is a project to make freely available to the scientific community a series of cerebral magnetic resonance imaging. The purpose of collecting and distributing freely MRI data sets, hopes to facilitate future discoveries in basic neuroscience and clinical research. OASIS is a project carried out at the Howard Hughes Medical Institute (HHMI) at Harvard University in the Neuroinformatics Research Group (NRG) at the School of Medicine of the University of Washington and the Network of Biomedical Informatics Research (BIRN). Despite following heterogeneous protocols in the acquisition of brain images, all follow a strict quality control.

Of these subjects, we know a set of data for cataloging, depending on their sex, age, preference for right or left hand, apart from a description of the subject's mental state based on criteria such as GDS (Global Deterioration Scale), CDR (Clinical Dementia Rating) or MMSE (Mini Mental State Examination).

It has been selected a set of MRI studies coming from these databases, which served as training and test of knowledge extraction algorithms used for generating classifier system. The distribution of subjects by sex and mental condition (normal, mild dementia) can be seen in Table 1 below:

Table 1 Data from the study subjects, per database used and total

	N	NORMAL	AD
ADNI	1514	766	748
OASIS	586	421	165
TOTAL	2100	1187	913

Brain imaging postprocessing was performed of the subjects mentioned above, using advanced techniques of quantification and morphometry of cerebral gray matter.

To ensure the greatest possible accuracy of the above parameters, special attention has been paid to the use of segmentation algorithms with low error and accurate registration techniques.

First, the segmentation is the classification of all image voxels, based on significant labels as "gray matter", "white matter" or even more specific, like "hippocampus", "thalamus" ... Errors in this phase result in the thickness or volume of different brain areas can not be calculated exactly, as it would take into account voxels not really corresponding with the type of tissue indicated by the segmentation. The algorithms used to segment brain volumes contain an error rate of around 12%. The algorithm developed for this study reduces the error of it to 8%, beating most common algorithms in this field, such as FAST[8], from package FSL [9], SPM [10], or FreeSurfer [11], as explained in the review article [7].

Furthermore, registering a subject brain volume with standard atlas is essential to label different anatomical regions of the brain. Any errors at this stage would cause parameters to be assigned to incorrect anatomical areas. They are therefore fundamental in population studies, to be able to compare the data obtained from a given subject with a certain population segment.

Our new implementation of Thirion algorithm [12,13], which, unlike other methods, registers the entire volume

(yielding much more information, and more precise than using only brain surface) with IBASPM atlas [14] in MNI space coordinates (MNI152 template specifically, of the Montreal Neurological Institute).

The use of the template MNI152 [15] allows labeling of 116 anatomical structures, both cortical and subcortical, 4 parameters calculated for each of them: average volume (cc) Average thickness (mm) and average fractal dimension, and local density (both measured dimensionless). Some of these parameters to specific brain regions are considered biomarkers for various diseases, according to studies published in journals [16].

Furthermore, it has been calculated, for each structure, the ratio between volume and total brain volume, dimensionless measure which indicates the percentage of the brain that occupies the structure. This makes a total of 580 parameters for each studied brain volume.

To create the system predictor of early AD, it has been used the implementation of decision trees using the method C4.5 [17] with MultiBoost technique. Using MultiBoosting is generated a series of decision trees for the same set of training, but random weights are assigned to each subject in the database in each of the various trees generated. The final classification is a combination by voting from different individual classifiers.

III. RESULTS

A. Degenerative Model with Respect to Age

The differences between healthy subjects and subjects with Alzheimer's disease, in terms of volumetric parameters in gray matter, follows a time course very characteristic. The highest volumetric differences occur in the early stages of the disease, whereas, with age, the differences tend to cancel.

Table 2 lists the major areas of the brain with structural changes, showing the significance (p-value) according to the age segment. You can see that the differences are more significant in the early stages, while in the following, differences cease to be.

B. Classifier and Predictive System

To evaluate this system, data obtained from the brain image processing of each subject is used as input along with study-specific data provided by the databases of images used. The output of the system represents the state of the subject ("normal" or "early AD").

The generated model may be expressed as simple logical rules. As an example, one of the rules generated by the system:

IF (AGE > 55) AND (TEMPORAL MIDDLE GYRUS THICKNESS <= 2.448985)
THEN CLASS = AD [PROBABILITY = 0.946]

In Table 3 below, we show the results of correct classification, sensitivity and specificity obtained by our algorithm.

Table 3 Validation Results.

Parameter	Value
Accuracy	91.48%
Sensitivity	90.80%
Specificity	92.30%

We see that the correct classification rate is over 90%, which makes the predictive power of the proposed model and algorithm is at least comparable to a mammogram [18].

IV. DISCUSSION

Given the need for a diagnostic method, we have developed a system capable of detecting early AD using MRI analysis with a high success rate, non-invasive, fast and objective. As sources of brain studies have used the ADNI and OASIS databases. The distribution of subjects by sex, age and condition is found in Table 1.

The first step was to generate a population model of the structural differences between healthy subjects and AD

Table 2 List of structures and significance (p) of the volumetric difference between healthy subjects and AD.

STRUCTURE	50	60	70	80
Paracentral Lobe (Right)	0.000	0.000	0.000	0.030
Paracentral Lobe (Left)	0.000	0.000	0.000	0.029
Postcentral Gyrus (Right)	0.000	0.000	0.000	0.003
Postcentral Gyrus (Left)	0.000	0.002	0.000	0.019
Precentral Gyrus (Right)	0.000	0.000	0.000	0.050
Angular Gyrus (Right)	0.000	0.000	0.001	0.016
Angular Gyrus (Left)	0.000	0.000	0.011	0.003
Calcarine Sulcus (Left)	0.000	0.000	0.043	0.134
Cuneus (Left)	0.000	0.000	0.043	0.057
Inferior Occipital Gyrus (Right)	0.000	0.005	0.008	0.007

patients. We have established which brain regions are those with the greatest differences (from the statistical point of view) in the evolution of AD compared to normal subjects, see Table 2. Also, we can see that the normal and AD in the elderly make these structural differences tend to disappear.

This degeneration model serves as the basis for the system of support to early diagnosis.

As a result of the validation on our database, we proved that the system's accuracy in classifying subjects as "healthy" or "AD" exceeds 90%, see Table 3. This indicates that it is a method with a high power predictive diagnosis, so that it could be considered as a screening method for early detection of AD even presymptomatic.

V. CONCLUSIONS

A good clinical history and application of a range of neuropsychological tests to assess the degree of impairment of various cognitive domains are of great importance for the diagnosis of AD. But this usually happens clinically when the AD is obvious (even in the slightest degree) and dementia has already appeared, and though there are effective treatments for the early stages of dementia, it is not possible to recover lost cognitive functions, or slow the progression of disease.

Hence, the importance of early detection of AD is undeniable, from the point of view both clinical and socioeconomic. Methods for early and accurate diagnosis of early stage of AD would, on one hand, delay or at least mitigate the loss of cognitive functions, and second, more effective development of drugs which only possible target so far, has been to change the course of this disease.

As future work, we see the integration of the results of neuroimaging processing with neuropsychological test results to create a population model, and predictive of AD from more information, correlating structural findings with cognitive / behavioral.

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