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ABSTRACT:

The Alzheimer’s disease (AD) is a disorder neurodegenerative, which is one of the most common causes of dementia in the older people, it constitutes one of the diseases with great social impact in Europe and America. The progress of medical diagnosis using magnetic resonance imaging (MRI) is widely used for the treatment of neurological diseases; it allows obtaining, increasingly, more functional and anatomical information from the brain of the patients, with a great precision in time and space. However, this big amount of data and images are impossible to analyze directly, is necessary to develop methodologies of calculus for quantified the parameters more relevant in the MRI.

This work proposes a methodology for the diagnosis of dementia based on Alzheimer’s disease combining imaging processing and artificial intelligence techniques. We created an artificial neural network (ANN) of classification based on architecture Multilayer Perceptron. In order to construct a complete dataset for training and testing of the network, initial inputs-target variables were obtained from the database OASIS (Open Access Series of imaging studies) with a total of instances equal to 235. The variables were classified into 3 groups: demographic, clinical and morphometric data. Task of training and testing were applied on initial data, obtained a 48% of confusion of the diagnosis. For minimize this percentages of error, image processing and Voxel based morphometry (VBM) techniques were implemented to obtain new morphometric variables of three areas of the brain: white matter (WM), gray matter (GM) and fluid (CSF) cerebro-espinal. In this way, we reduced the percentage of confusion to 17%. The results obtained with the ANN, demonstrated that the demographic and clinical information from patients, combined with morphometric information of areas of the brain, are input variables useful to train an ANN of diagnosis of dementia with 83% of reliability, and in this way, help to the early diagnosis of AD.

KEYWORDS: Medical imaging processing, segmentation, neural network (ANN), Magnetic resonance imaging (MRI), tissues of brain, Alzheimer’s disease (AD), Voxel based morphometry (VBM), Multilayer Perceptron.

1 INTRODUCTION

AD is a disorder neurodegenerative, which is one of the causes of most common dementia in the elderly, also constitutes one of the diseases with great social impact in Europe and America.

Although AD is not a normal success of old age population, the risk of developing this disease increases in elderly persons. For the past 2005, in Europe were diagnosed 3600,000 patients affected by AD (source: Frost & Sullivan) and in recent research carried by Alzheimer Europe, was estimated that 7.3 million people have dementia.

Normally, the diagnosis of AD is done after the exclusion of other forms of dementia, but the definitive diagnosis requires not only the presence of large cognitive deficits in patients, also require the confirmation in the autopsy, which consist in a study of brain tissue.

Under these circumstances, the early diagnosis of dementia establishes new goals in clinical research of AD (Morris, Storandt, et al. 2001) (Mueller, Weiner, et al. 2005b). Numerous studies based on magnetic resonance imaging (MRI) are used to describe the differences of the brain structure between demented patients and healthy subjects (Jack, et al. 1997) (Killiany, et al. 2002) (Morra, et al. 2008), being the main objective to find degree of relation between brain abnormalities and development of the disease.

In this paper, we describe a methodology to combine medical images processing, VBM and ANN techniques for the diagnosis of dementia based on AD, making the task of diagnosis as a problem of classification using the Clinical Dementia Rating
(CDR) (Morris 1993) as output of the network. The inputs-targets variables for the training and testing of the ANN were obtained from a free database of MRI aimed at research of AD. In order to improve the results of diagnosis, techniques of image processing and VBM were applied into MRI datasets to extract numerical information of affected brain tissues.

The figure 1 shows the stages implicated in the development of diagnostic ANN of AD, from obtaining initial datasets until building the ANN.

2 MATERIALS AND METHODS

2.1. Obtaining the initial dataset and inputs-target variables from OASIS database

Obtain successful results in the training and testing of the network depends on the proper choice of variables and a sufficient sample of instances. In order to obtain these, we used the datasets of brain MRI with clinical and demographic data of subject provided by OASIS (Marcus, et al. 2010), which is a project aimed at making MRI datasets of the brain freely available to the neurology researches. This dataset included 235 cross-sectional collections of 416 subjects aged 18 to 96 years (where 100 the included subjects older than 60 years have been clinically diagnosed with very mild to moderate AD).

In the first stage, all variables of OASIS database were used to integrate three groups of data: a) demographic data integrated by sex(1), age(2), Handedness(3), education(4), socio-economic status (SES) (5); (b) Clinic data integrated by Mini-Mental State Examination (MMSE)(6) and Clinical Dementia Rating (CDR)(7); and c) morphologic data conformed with eTIV (Estimated total intracranial volume) (Buckner, et al. 2004)(8), (Fotenos, et al. 2005); nWBV (Normalized whole brain volume, nWBV) (Fotenos, et al. 2005)(9), y (3) ASF (Atlas Scaling Factor) (Fotenos, et al. 2005) (10), which is a factor of increase or decrease of the volume of the brain to be registered to an atlas-template supplied by Talairach and Tournoux (Talairach and Tournoux 1988).

The CDR factor constituted the target variable of ANN, it was developed at the Memory and Aging Project at Washington University School of Medicine in 1979 and it is used in both research and clinical settings to characterize the level of cognitive and functional performance in patients at risk for or suspected of having AD or another dementing disorder. In clinic diagnosis, the CDR score is calculated by standard algorithm and its possible values are: CDR=0: no impairment; CDR=0.5: very mild; CDR=1: mild; CDR=2: moderate; and CDR=3: severe dementia. However, as the database used only had two instances with CDR =2 and zero instances with CDR=3, in this work was used the dataset with CDR=0, 0.5, 1 y 2.

- Additional brain morphological parameters obtained using image processing techniques

Research in neurology have shown that the volume of the brain and the zones involved in memory have a significant degree of atrophy in patients with mild cognitive impairment (MCI) and early stages of AD (Jack, et al. 1997), (Killiany, et al. 2002), (Fotenos, et al. 2005), (Morra, et al. 2008). Based on this, we decided complemented the morphometric group obtaining the total volume of important brain tissues: white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF).

The brain tissues are characterized by a varied, complex and often overlapping morphology, for these reasons, the task of obtain precise volumes for statistical and morphometric studies is not an easy and trivial task. In order to obtain them, we applied techniques of image processing, which were implemented in four stages: (a) reading and three-dimensional reconstruction of each cross-section of MRI; (b) Preprocessing, to remove artifacts and improve the quality of the images; (c) Segmentation of three tissues of interest and (d) quantification of the volumes segmented, using techniques of Voxel based Morphometry (VBM). The workflow of algorithms used for obtain the volumes is based in the methodology presented in (Gavidia, et al. 2011).

After obtain the three volumes, were calculated the total number of voxels of WM (voxels_WM), the total number of voxels of GM (voxels_GM) and the total number voxels of CSF (voxels_CSF). Then, were calculated the percentage of tissue for each one relative to the sum of three amounts referred above total volumes (total_voxels), see ec. 1. On this way, were obtained three new inputs-variables: %WM, %GM and %CSF, which were included into morphometric group.

\[
\begin{align*}
\% WM &= \frac{1}{\text{total_voxel}} \\
\% GM &= \frac{1}{\text{total_voxel}} \\
\% CSF &= \frac{1}{\text{total_voxel}}
\end{align*}
\]  

(ec. 1)
- Analysis of the input-target variables

In the previous sections, we described how we obtained 12 initial variables (9 inputs and 1 target) from OASIS database. The current stage consisted in calculate the correlation between the inputs variables and target variable, analyzing their values and determine their dependence. This process showed that Handedness, Education and SES variables have not a correlation clearly defined with the rest of variables. Also, the analysis showed that nWBV and ASF variables could be eliminated because not provided relevant information to the training. The first one is implicit in the sum of %_WM and %_GM variables and the second one is equal to 1755 divided by eTIV variable (Buckner, et al. 2004). Thus, this stage allowed us to establish that nine of twelve initial variables could be more suitable for training and testing of the ANN, however, the definitive exclusion of these variables only will be confirm in the phase of training and testing by compare the confusion percentage de la ANN using different groups of variables.

2.2. Artificial neural network training

At this stage, we determined the characteristics and functionalities would be applied in the training of the ANN

- Selection of the rule of learning and training algorithm

First, was necessary to determine the type of rule of learning and the training most appropriate to solve our problem of diagnosis. Given that the same occurrence of the set of inputs always will be associated to a specific target, that is, the occurrence of certain values in each one of the 12 inputs should correspond to a same diagnosis CDR (target), we decided establish the problem of diagnosis as a problem of classification. Likewise, based in the nature of the problem, we decided use the Multilayer Perceptron, which is a type of supervised learning network and as task of learning was selected the Pattern Recognition technique, widely used in the solution of problems of classification. In the practice, pattern recognition approach compared the obtained outputs with the correct target, by adjusting the weights (W) and biases (b) of the network and ensures that the outputs were closer to the target. Figure 2 shows a general scheme of the ANN architecture implemented in this research.

Figure 2. General scheme of the ANN architecture

- Training of the network

The main tasks were:

a) The dataset pre-processing. All inputs-targets were normalized in the interval [-1 1];

b) Division of the data. The dataset was divided in two groups, the first one was used in the training with 80% of total sample and the second one was
used in the testing with 20% remaining. This division of data was done randomly.

(c) Determine the architecture of ANN most effective, by setting the number of entry layers and hidden layers.

(d) Training and testing of the network, these processes were repeated until to find the weights and biases more adequate for minimize the percentage of confusion between targets and obtained outputs. Likewise, this step allowed us establishes definitely which combinations of inputs variables were more suitable for diagnosis of dementia.

(e) Post-processing of the outputs, the continuous values obtained as output were post processed to locate into any of the four classes of CDR target.

3 RESULTS

In the testing process applied to three different groups of inputs, the results confirmed the assertions done in the previous section about the correlation between variables and the importance of considering information about the size of affected brain tissues in patients with AD:

(a) Group of original nine inputs from OASIS database (Sex, handedness, age, education, SES, MMSE, eTIV, nWBV, ASF) was obtained 48% of confusion error, that is, only 122 of 235 diagnostics were correct;

(b) Group of 6 inputs without additional morphometric data (Sex, age, MMSE, eTIV, nWBV, ASF), gave a 25% of confusion error, that is, only 122 of 235 diagnostics were correct.

(c) Group of 7 inputs variables including additional morphometric inputs (Sex, age, MMSE, eTIV, %_WM, %_GM(13),%CSF), gave a 17% confusion error.

The figure 3 shows the regression plot of the results obtained in the testing of ANN showing normalized values to CDR: CDR=0→-1, CDR=0.5→-0.5, CDR=1→0, CDR=2→1. The dashed line in each axis represents the perfect result, the solid line represents the best fit linear regression line between outputs and targets. The $R$ value is an indication of the relationship between the outputs and targets. If the training were perfect, the network outputs and the targets would be exactly equal, that is $R=1$, but the relationship is rarely perfect in practice. For this research, using the third group of variables, the testing data indicated $R$ value that greater than 0.8, which is a good result. The plot showed that certain data points have poor fits, for example, there are data points in whose output values are close to -0.5 (CDR=0.5: very mild), while the corresponding target values are about -1 (CDR=0: no impairment); in another case, there are data points in whose output values are close to 0.5 (CDR=1: mild dementia), while the corresponding target values are about 1 (CDR=2: moderate dementia). A possible reason to this confusion could be the extrapolation of some instances outside of the training dataset, which is comprehensible given the small number of instances to CDR=2.

![Figure 3](image-url)
input variables (Sex, age, MMSE, eTIV, nWBV, ASF). (c) 17% confusion (195/235) obtained in testing applied to 235 instances with seven input variables (Sex, age, MMSE, eTIV, %_WM, %_GM, %CSF). (Plots obtained using Neural Network Toolbox of MATLAB) (R2009b 2011)

4 CONCLUSIONS

Through this research was demonstrated that the combination of appropriate demographic, clinical and morphometric brain data of a patient obtained with medical imaging processing and VBM techniques are inputs suitable to build a successful ANN of diagnosis of AD.

The ANN learned from MRI data in 235 cases. In the general testing, the percentage of confusion was 17%, this error indicates that only 195 of 235 cases were incorrectly diagnosed. However, the existence of small error rate reflects that always is necessary the continuous monitoring of the ANN diagnosis by an expert in neurology.

This research has some limitations. The experimental data sample is small and maybe the number of variables is limited. In order to improve the results of diagnosis of CDR, it is necessary to collect more samples from other brain database, for example, include datasets from Alzheimer's Disease Neuroimaging Initiative (ADNI) (Mueller, Weiner, et al., 2005a), (Mueller, Weiner, et al., 2005b). Also, studies dedicated to investigate atrophied brain by AD, make reference to another areas affected by this disease as the ventricles, the hypothalamus and the sea-horses (Morra, et al. 2008). Thus, it is possible to obtain better results in the diagnosis of dementia including new morphometric inputs. Additionally, could be considered statistical descriptors (entropy, correlation, standard deviation, etc, calculated) from segmented volumes of the brain.

Finally, we believe that the methodology applied to build the ANN with the monitoring by medical personal, could be applied to another type of pathological diagnosis.

REFERENCIAS


