Complex relationships between structural changes using brain Magnetic Resonance imaging in early diagnosis of Alzheimer’s Disease

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“I have not failed. I’ve just found 10,000 ways that won’t work.”

*Thomas A. Edison*
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Abstract

Neurodegenerative disease is the term used for a sort of incurable pathologies present in the brain. It results in progressive degeneration of nerve cells, leading to movement ataxias, or mental dementias. Dementias are responsible for greatest burden of disease with Alzheimer’s representing approximately 60-70% of cases. The main goal of this thesis is to highlight subtle anatomical differences that constitute abnormal structural patterns that may indicate the presence or absence of the pathology in regions with similar visual features by using Brain Magnetic Resonance Imaging.

Keywords: Magnetic Resonance Imaging, Visual Attention Models, probabilistic Latent Semantic Analysis, Alzheimer’s disease, Neurodegenerative diseases

Resumen

Enfermedad neurodegenerativa es un término utilizado en una amplia gama de patologías presentes en el cerebro que son incurables, estas resultan en la degeneración progresiva o destrucción de células nerviosas. Llevando a problemas con el movimiento ataxias, o el funcionamiento mental demencias. Las demencias son responsables de la mayor cantidad de personas afectadas. La enfermedad de Alzheimer representa aproximadamente el 60-70% de los casos. El objetivo principal de esta tesis es resaltar diferencias anatómicas sutiles que podrían constituir patrones estructurales anormales que permitan indicar la presencia o ausencia de la patología en las regiones con características visuales similares mediante el uso de la resonancia magnética cerebral.

Palabras Clave: Imágenes de Resonancia Magnética, Modelos de Atención Visual, Análisis Probabilístico de semántica latente, Enfermedad de Alzheimer, Enfermedades Neurodegenerativas
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1 Theoretical Framework

Higher brain functions are supported by one or more neural networks which are not necessarily contiguous i.e., brain regions can be differently affected by neurodegenerative diseases with different clinical onsets. Alzheimer’s dementia (AD) is the typical example of a disease that primarily affects higher brain functions, it is also the most common type of dementia, affecting over 20 million people in the world.

Currently, an effective technique or bio-marker to detect AD in early stages is not yet available. Usually, neurological and neuropsychological information obtained from clinical evaluation of patients and relatives are collected and analyzed to detect this pathology. However, this procedure allows to diagnose probable Alzheimer when the disease is already advanced, impeding any possibility for patients to change their lifestyle and prevent the evolution of this pathology.

Nowadays, neuroimaging plays an important role in early diagnosis of AD, by extracting useful information and relations from structural (Magnetic Resonance Imaging, MRI), functional (Functional MRI, fMRI) and blood perfusion (Single-Photon Emission Computed Tomography, SPECT) modalities, among others. In MRI, structural changes in brain regions, such as atrophy, become evident during the disease progression. In particular, initial analysis of these images has shown that hippocampal atrophy is one of the first structural manifestations of this disease: for patients previously diagnosed with mild AD, the Hippocampus area has been reduced in about 15% to 25%, compared to healthy patients. This atrophy could be detectable five years before symptoms. However, when structural imaging is used for early AD diagnostic the differences between aging brain and AD patients bare complex, because all brains are morphometrically different; this issue could lead to establish an incorrect identification of the pathology stages.

This thesis proposes a novel method to identify similar visual features in brain magnetic resonance images to find discriminant patterns. It starts by extracting low-level features from brain MRI, to describe each volume as a co-occurrence histogram of visual features. Upon this description, we attempt to find the underlying structure of the information, as separated regions with low level similarity. The third step involves the independent application of a visual attention model onto these regions, to identify relevant visual information within each region. Finally, a Support Vector Machine classifier is trained, in order to separate
1.1 Alzheimer’s Disease and brain morphometry

Alzheimer’s Disease (AD) is a common neurodegenerative brain disorder that damages and destroys brain cells; it leads to memory loss, personality changes, and problems with communication. The first person who described AD was the German neurologist Alois Alzheimer, in 1906 [12]. He presented a case of a woman with early dementia and other symptoms. She was institutionalized when she became unmanageable, some years after her initial symptoms she died. Her autopsy revealed a serious atrophy of the cortex in different areas. Alzheimer found sclerotic plaques scattered through the entire cortex. He also noted that many of the cortical neurons were reduced to dense cumulus of neurofibrils, these descriptions made by Alzheimer sprang up a new branch of pathology. Five years later, 11 similar cases of pre-senile dementia with neuropathological plaques and tangles were reported in the medical literature [2], but the official confirmation of this disease as unique was attributed to Emil Kraepelin. He described the AD as a subtype of senile dementia and pre-senile dementia. Nowadays, dementia is recognized as a basic feature of this disease, but its causes remain unknown. [12] However there are some features that may have incidence: Cortical Atrophy, neuronal cell death, amyloid plaques and neurofibrillary tangles. Some hypotheses declare that initial stage starts in the entorhinal cortex of Hippocampus, where the disease spreads to the temporal and the frontal cortex. At final stages the entire brain is affected but the greatest damage remains in the place where the disease started.
The physio-pathological process of AD begins many years before the first diagnosis of dementia. [22] The patient does not present any memory loss and an interview with a doctor will not determine any symptom. The second stage is called Very mild cognitive decline. In this period the person may have memory lapses and can forget common things, but no symptoms can be detected. The third stage is called Mild cognitive decline, a phase with symptoms, but not present at all patients. People that surround the affected person starts to detect difficulties regarding task performance at work and at home. Doctors may detect these difficulties by making a medical interview and may find memory or concentration problems.

The fourth stage is called Moderate cognitive decline. [17] The doctor may detect some symptoms by making an interview to apply psychological and cognitive tests. Some indicators related to this stage may demonstrate problems to remember recent events, inability to perform mental arithmetic calculations, problems planning and executing tasks and becoming irritable or withdraw in public with a challenging situation. Moderately severe cognitive decline is the fifth stage, the affected person starts to have some memory gaps that are noticeable and begin to need help in some routine activities. This is a moderate stage of AD. The sixth stage known as severe cognitive decline memory loss continues to worsen, it also starts to have personality disorders and need help with all daily activities.

1.1.1 Diagnosis

The common method to detect probable Alzheimer Disease is with the patient medical history [6], history from relatives and clinical observations. Specialist seeks for neurological and neuropsychological features but this examination method only detects AD when the disease is in advanced stage. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Association established some criteria called NINCDS-ADRDA Alzheimer’s Criteria. This standard updated on 2007 and requires to be confirmed by neuropsychological test. This exam finds the presence of mild cognitive impairment (MCI) \(^1\) and the suspicion of dementia syndrome. If those symptoms are found, the clinical diagnosis will be possible or probable AD. A histopathologic confirmation, including a microscopic examination of the brain tissue, is required for a definitive diagnosis.

Another criteria was issued by the American Psychiatric Association, called The Diagnostic and Statistical Manual of Mental Disorders (DSM). It provides a standard criterion to classify mental disorders. The manual DSM-IV was published in 1994 and it was revised on

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\(^1\)MCI: Brain-function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities
1.1 Alzheimer’s Disease and brain morphometry

2000, a new revision is planned to be published on 2013. These criteria establish a system in which the symptoms categorize the type of dementia. It is comprised in 5 categories (Axis I, Axis II, Axis III, Axis IV and Axis V) in Axis I, the major mental disorders are presented including mental and clinical disorders, like Anxiety and Depressed Mood. Axis II is conformed by personality disorders and intellectual disabilities disorders, such as Autism, Axis III contains acute medical conditions and physical disorders such as AD, In Axis IV, there are classified Psychosocial and environmental factors that contribute to the disorder like job loss. Finally Axis V contains Children’s Global Assessment Scale for children and teens under the age of 18.

Current diagnosis of AD relies on mental decline but it is known that the disease causes several brain damage. There are currently no validated biomarkers for Alzheimer’s disease, but there are some tests that will help to make a diagnosis of probable AD.

1.1.2 Genetic tests

Three genes have been identified with variations that will probably cause AD. These genes increase the risk, but do not guarantee that a person will develop the disease. The Apolipoprotein (APOE) [19] is associated with vulnerabilities of medial temporal lobe structures, but there are no treatments yet available that can change the course of AD. The second is the Amyloid precursor protein (APP) [3] whose function is yet unknown. There are some hypotheses that relate the protein as a regulator of the synapse formation. It is also studied as the responsible generator of beta amyloid that is the primary component of amyloid plaques found in the brains with AD patients. The mutation on the Presenilin gene [16] is associated with inherited Alzheimer’s, which runs in families and can strike people in their 30s. It also performs the function that enables cells to digest unwanted proteins and is essential for brain cell survival. The mutation interrupts this cellular protein-recycling process, killing nerve cells.

1.1.3 Imaging diagnosis

The advance on Neuroimaging techniques introduce accurate non-invasive biomarkers, associated structural changes in the brain of patients with AD. Some alterations could be

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3A Numeric scale used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults, e.g., how well or adaptively one is meeting various problems-in-living
4ApoE, the protein coded by the APOE gene, is a lipid transport protein implicated in maintenance and reparation of neuronal cells
visible like the Hippocampus reduction. A functional imaging technique provides information about alterations that can be produced by AD, like reduction on the glucose metabolism and bloodstream in some regions of the brain. [18] There is not another method to make a diagnosis using just a single technique.

**Computed tomography (CT)**
Computed tomography (CT) is a medical imaging procedure that uses computer-processed X-rays images. [11] A Computed tomography provides more information than a single x-ray and can show differences between structural changes. Alzheimer disease affects the Temporal Lobe [14] and the Hippocampus. These changes can be detected win CT. Nowadays; these images are not able to detect patterns that can be used in the diagnosis, but they attempt to dismiss other dementia causes.

**Magnetic resonance imaging (MRI)**
MRI is a medical imaging procedure which helps to visualize internal structures of the body in detail. Initially, MRI was used to exclude conditions such as Brain tumors or Hematomas, but nowadays it helps to identify and measure changes in brain structure, like Media temporal lobe atrophy, which predicts the progression of MCI to AD. It also identifies features in brain structure through time showing the neuronal destruction produced by the disease. The most established marker that identifies an AD pathology is the atrophy of the Hippocampus. This damage can be measured through the brain volume, in mild AD the hippocampus reduce its volume by 15-25 percent [9], when comparing to healthy patients. These studies show that atrophy may be detectable five years before symptoms. However the main disadvantage using MRI is when the studied population does not represent typical AD patients, because some subjects with detectable Vascular Pathologies may be excluded.[8]

**Diffusion tensor imaging**
Diffusion Tensor Imaging (DTI) is a MRI technique method; it was developed in mid-1980s. [7] It allows mapping the diffusion process of water molecules. Molecular diffusion is not free, because it reflects interactions, such as macromolecules, fibers, membranes, among others. These molecules can reveal details about the tissue architecture showing white matter disorders and providing models of brain connectivity.

There are some evidences [21] that changes in white matter will be probably related to specific cognitive dysfunction. These structural changes are found in all lobes of the brain, but it is most prominent in the frontal white matter. Find these differences between control and affected brains will help to have more information about the disease’s behavior and how to prevent it.
1.2 Morphometry

**Positron emission tomography (PET)**
Positron emission tomography PET is a nuclear medicine imaging technique, that produces 3D images of functional processes in the body. The machine tracks pairs of gamma rays emitted indirectly by a positron-emitting radionuclide, which is introduced into the body, then 3D images are reconstructed by computer analysis, it also shows how brain regions are working by displaying how the cells use sugar or oxygen. The radiopharmaceutical component used to find Alzheimer’s disease [15] changes is known as 18F-fluorodeoxyglucose, this molecule is a glucose analog that is attracted by cells, then when it is inside of them suffers metabolic processes and displays the way the glucose is being used in tissues.

AD is often associated with reduced use of glucose in brain areas important in memory, learning and problem solving. In 2004 the compound [N-methyl-11C] 2 - (4’-methylaminophenol) - 6-hydroxybenzotriazole was developed to join amyloid plaques, highlighting senile plaques of aging brains. The component received the name of Pittsburg Compound-B (PIB) [20] the images show that AD patients have an accumulation of PIB component in contrast to controls.

**Functional magnetic resonance imaging (fMRI)**
Functional Magnetic Resonance Imaging mixes images of MRI with regions that are activated in the brain in response to a sensory stimulus or a cognitive task by comparing images obtained in repose periods with images obtained during the stimulus, an activation brain map is resulted. [18] fMRI measures oxygen level in the brain blood, those changes are associated with the stimuli. This information is helpful to obtain images to study brain functions without a contrast agent. Its main contribution is that unlike PET scans, it is important to treat them as a timeseries. Because the BOLD signal will tend to be correlated across successive scans, meaning that they can no longer be treated as independent samples. This technique helps to make comparisons between controls and AD patients. Analyzing the region activation (media temporal lobe, where structures are related to memory like hippocampus) when a stimuli is produced.

**1.2 Morphometry**
Morphometry [20] can be defined as the application of statistical procedures to analyze the variability in in size and shape of organs and organisms, can be used to quantify changes in fossils, human anatomy, between ecological factors and biology among others. The relation between shape and function had led many researchers to find methods that describe quantitatively structures or forms, like Pythagoras, he used to draw animals and plants by noting the number of junctions between the lines of the sketch. The relation with morphometry and geometry was first described by Albrecht Durer an artist of the 15th century. He use
the properties of affine transformations for distorting details by lateral or vertical elongation, thus mapping a square into a parallelogram and, or, by sharing a feature. In 1957 professor Robert E. Blackith [25] uses basic principles of morphometry to explain the demographic explosion of locusts.

In late years, researchers have developed tools to understand the human body. Brain morphometry [24] is the result of combining technologies; it uses digital medical images, computer tools, mathematics and statistics to analyze changes on brain structures. Features found by this analysis help to understand brain changes during the time, namely; development, aging, learning and evolution. These diseases can be characterized by quantifying anatomical features of the brain (shape, mass, volume), revealing changes in white matter connectivity and cortical thickness among others. These markers might be used for the early management of the disease.

The Voxel-based morphometry (VBM) [1] method calculates local differences between brain volumes, by making scans of MRI and normalizing it into a stereotactic template, the 2-D slices are used to reconstruct the image of the brain in 3D and the regions of interest (ROI) are compared and segmented to find differences between groups. This comparison is statistical mapped, analyzed and interpreted. It provides enough data to generate hypotheses of brain changes, helpful to understand changes that occur in AD patients. The problem with this technique is that the shape and size of human brains are very different between subjects. Moreover the images from a subject may not be comparable because the orientation variability (head position) within slices. This variety of noise sources affects the results of the statistical analysis and so the mapping. The other main problem is the level detail in the images and high resolution are not cost effective low resolution the risk of missing important details increases.

The Deformation-based morphometry method [27] analyze information coming from the deformations fields obtained by nonlinear registration of brain MR images this technique aims to detect morphological differences over the brain since it analyses positional differences between voxels and a standard template brain MRI. It is also used to estimate brain atrophy through time, by labeling the interest structures.

Feature-Based Morphometry (FBM) [23] has been proposed to cope anatomical variability within subjects, by extracting and identifying anatomical patterns that are statistically significant, and characterizing them as local features that replaces the global template for morphometry analyzes.
1.3 Finding patterns on brain morphometry

Brain morphometry has been traditionally used to discover changes among the brain structure, some them associated to abnormal patterns. Yet most of the morphometry methods measure brain regions under the underlying assumption of local statistical independence, this hypothesis look quite inconsistent since the brain is not just a spatial locus but rather a set of functions distributed onto a net of spatial regions, usually separated. The particular pattern defined by the configuration of the net may constitute the early signs of some degenerative diseases. This statement led us to search for techniques that might group regions under different types of metrics, that is to say, not just by connecting neighboring regions. Among a large group of clustering methods that could group common visual features and find complex relations, Probabilistic Latent Semantic Analysis, (PLSA) is advantageous because it may softly group features while maintaining a sort of uncertainty by the irregular borders of the resultant partition. It was firstly proposed by Jan Puzicha and Thomas Hofmann [13] in 1999, the method is based on a statistical latent class model of three variables; documents, words and topics. The idea is to represent documents as vectors, and each vector entry corresponds to the number of times a word appears in the document, resulting in a co-occurrence matrix. This mapping determines a set of hidden topics in the document by analyzing the frequency of each word, using that co-occurrence matrix. The technique can be applied in text learning and information retrieval. In our case PLSA, determines relationships between hidden topics [5]. The geometric patterns correspond to visual words and the analysis, by means of the co-occurrence, establishes the visual topics. The whole framework defines a generative model of complex anatomical relationships by clustering brain regions with similar local features, not necessarily with anatomical meaning. In Figure 1-2. The proposed approach is described.

This first step starts then when the data set is split into test and train sets. For each image of the training set, information about edges and orientation is extracted by two different filters: Gabor and sobel. The former extracts orientation features in four different directions: $0^\circ$, $45^\circ$, $90^\circ$ and $135^\circ$, while the latter obtains edge features in horizontal and vertical directions, using a $3 \times 3$ and $5 \times 5$ Sobel filters. Once the image is filtered out and two new images, orientation and edges, are obtained, each of the two images is split into patches that constitute the basic visual words of the visual vocabulary. Likewise, the visual documents are larger patches with anatomical meaning, in this case was a patch that might cover a real anatomical region, typically of $60 \times 60$ pixels. Each “visual word” is then searched in each “visual document” to construct a co-occurrence histogram. Now, each visual document is modeled as a mixture of topics as a joint variable $(d, w)$ that is independently sampled:

$$
P(d_i, w_j) = P(d_i)P(w_j|d_i), \quad P(w_j|d_i) = \sum_{l=1}^{k} P(w_j|z_l)P(z_l|d_i),$$

(1-1)
Where $d_i$ is the $i$-th visual document, $w_j$ the $j$-th visual word and $z_l$ is the $l$-th latent topic, manually selected. As the topic distribution is not an observed variable, the probability of the unobservable distributions $P(z_l|d_i)$ and $P(w_j|z_l)$ can be learned from the likelihood:

$$L = \prod_{j=1}^{N} \prod_{i=1}^{M} P(w_j|d_i)^{n(w_j|d_i)},$$

(1-2)

where $N$ is the number of visual documents in the slice, $M$ is the number of visual words in the visual vocabulary, $n(w_j, d_i)$ is the number of visual word occurrences in a visual document $d_i$ and $P(w_j|d_i)$ is given by Equation 1-1. The Expectation-Maximization (EM) algorithm is used to estimated the best model parameters, estimating all the posterior probabilities for the latent variables $P(z_l|d,w_j)$, while optimizing $P(w_j|z_l)$ and $P(z_l|d_i)$. This algorithm is implemented as an iterative process that stops when reaching convergence.
1.4 Regional Saliency Maps

Given the regional partition obtained from the probabilistic approach, each region is masked with the original brain volume. The regional relevant information is determined with a Visual Attention Model, an analytical tool that mimics the attentional process and that performs a multiscale correlation of the information flow. These models reveal salient regions in an image by analyzing low level features like the orientation or the particular edge pattern. Visual attention models (VAM) were firstly introduced in 1976 [4] by the artificial vision community and have evolved since.

The VAM used in this thesis is known as Graph-Based Visual Saliency (GBVS)[10], which basically models the image information as a fully connected graphs whose edges establish the type of connection between two nodes. The method attempts to emulate a radiologist when examining medical images, by including a semantic notion of dissimilarity between image pixels (nodes).

Graph Based Visual Saliency includes three steps to calculate saliency maps: feature extraction, activation maps and combination. The first step uses the regions set by the PLSA clustering, as depicted in Figure 1-3. Then, a fully-connected graph is constructed on each of these regions, storing the dissimilarity information between nodes (pixels) in the edges. This relationship between pixels is regularized by a closeness notion, modeled using a Gauss-
sian function. The activation maps, that correspond to the set of more dissimilar pixels within a region, are estimated by constructing a Markov Chain onto the graph and calculating its equilibrium distribution as the principal eigenvector of the transition matrix of the graph. Finally, the normalized activation maps are first averaged per feature channel and then combined together into a single master saliency map per region, as illustrated in Figure 1-4.

![Figure 1-4: Construction of regional saliency maps.](image)

### 1.5 Classification and Anatomical Interpretation

The last step of the proposed method involves a machine learning analysis. Machine learning (ML) [26] is a set of techniques or framework that can establish a sort of boundary between two datasets by learning from the very inner data structure. This framework helps to automatically recognize complex patterns and make decisions using a set of examples. A natural limitation of this type of strategies comes from the inaccuracy at making some of these decisions, basically because of the variability of the studied system or the capturing device that may introduce different kinds of noise. A very convenient approach to this kind of problems is the statistical analysis, which starts by mapping a particular model with the observations, the likelihood function. Maximum Likelihood (ML) or maximization of that function aims to capture characteristics of interest in the data, establishing statistical based relations between the observed variables. A particular case of such approach is the Support Vector Machine, a learning machine that sets a boundary between two classes by using the information of those samples closer to the boundary.

A Support Vector Machine (SVM) is herein used because it is able to learn an ill-healthy boundary and classify the pathological and normal subjects. In addition, This strategy serves to identify the anatomical regions that are relevant for classification and correspond to those samples closer to the boundary or the support vectors. The main contribution
of this work, is that the presented method not only allows to classify structural brain MRI but rather to highlight anatomical areas related with a probable pathology, achieving clinical interpretability. This method finds a quantitative estimate of brain differences, an important issue in the clinical management of the Alzheimer’s disease.

This step starts by using two classes: AD (Alzheimer’s disease) and NC (normal control), whose brain data are mapped to the space of visual saliency maps and used as the input to train the SVM classifier. As the SVM approach requires a kernel function, which acts as a nonlinear mapping from an input space to a feature (separable) space, a similarity measure is here used to precompute the kernel. To do so, the regional saliency maps are first individually normalized (to resemble a histogram) and then compared (in a one-to-one fashion) using the histogram intersection:

$$H_{\text{int}}(A, B) = \sum_i \sum_j \min\{A(i, j), B(i, j)\}$$  \hspace{1cm} (1-3)

The obtained values range from 0 (no overlapping or intersection) to 1 (complete overlapping or intersection), giving as a result a kernel matrix which feeds the SVM classifier. An initial cross validation is performed to adjust the value of the penalty parameter $C$, and with the optimal value, the final classification of the brain MR Images is performed.

Using the weights of the support vectors that define the separating hyperplane of the SVM, a quantitative estimate of the brain differences can be established. It allows to identify most relevant regions for pathological discrimination, by using their coefficient values (positive for normal controls and negative for pathological subjects). The relevant regions can be visualized in an averaged discrimination relevance map by performing a linear combination of the regional saliency maps and their corresponding coefficients, encoding with different colors the positive (normal) and negative (pathological) contributions. Finally, these regions are correlated with anatomical areas, using the Harvard-Oxford atlas [16] to label the regions of interest with 96 cortical and 21 subcortical structural areas. For each anatomical region, the mean value of the discrimination relevance map is stored, allowing to quantify the importance of each anatomical area.
2 Classification of Alzheimer’s Disease using Regional Saliency Maps from Brain MR Images

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Classification of Alzheimer’s Disease using Regional Saliency Maps from Brain MR Images

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Abstract. The main problem in the diagnosis of the Alzheimer’s disease is the complex alteration patterns that indicates the presence or absence of the pathology. Actually, an effective and accurate method that allows to interpret the disease in terms of global and local changes is not available in the clinical practice. In this paper, we propose a methodology based on combining a probabilistical technique, that construct image regions using latent topics inferred from brain Magnetic Resonance images, with a visual attention model that extracts saliency maps of relevant information per region. Comparison of the combined saliency maps allows to classify the images into normal or pathological subjects. Preliminary results show that the proposed method reaches a classification accuracy of 75%, allowing to relate local changes that are occurring in different regions of the brain.

Keywords: Alzheimer’s disease, MRI, Attention Models, Morphometry, PLSA

1 INTRODUCTION

Alzheimer’s disease (AD) is the most common type of dementia, affecting over 20 millions of people in the world. Currently, an effective technique or biomarker to detect AD in early stages is not yet available. Usually, neurological and neuropsychological information coming from the patient history, [1] history from relatives and clinical observations is collected and analyzed to detect Alzheimer’s Disease. However, this procedure allows to diagnose AD when the disease is in an advanced stage, impeding any possibility for the patient to change their lifestyle and prevent the evolution of this pathology. Nowadays, neuroimaging research plays an important role in the early diagnosis of AD, by extracting useful information and relations from structural (Magnetic Resonance Imaging, MRI), functional (Functional MRI, fMRI) and blood perfusion (Single-Photon Emission Computed Tomography, SPECT) data, among others. In MRI, structural changes in brain regions, such as atrophy, become evident during the disease progression. In particular, initial analysis of these images have shown that hippocampal atrophy is one of the first manifestations of the disease: for patients previously diagnosed with mild AD, the hippocampus area has been reduced
about 15% to 25%, compared to healthy patients [2], showing also that this atrophy may be detectable five years before symptoms.

To extract and analyze patterns of structural change in brain MR images associated to neurological pathologies, currently the most used techniques are known as Voxel-Based Morphometry (VBM) [3] and Deformation-Based Morphometry (DBM) [4]. In VBM, local differences in brain tissue segmentations are statistically analyzed voxel-by-voxel by normalizing each volume into a stereotactic template, while DBM analyses information coming from the deformations fields obtained after registration to the template. With these methods, one-to-one correspondences between subjects are assumed to effectively analyze the volume information, assumption that could not be true due to the intrinsic anatomical variability within subjects. Recently, Feature-Based Morphometry (FBM) [5] has been proposed to cope with this issue, by extracting and identifying anatomical patterns that are statistically significant, and characterizing them as local features that replaces the global template for morphometry analyses. This approach has been tested over the OASIS data set [11], achieving a maximum classification performance of 0.80 in the Equal Error Rate measure. Another classification approach has been proposed in [9], where the brain images are decomposed into basis functions by means of an Independent Component Analysis (ICA) technique, information which fed a Support Vector Machine (SVM) classifier. Experimental results on the OASIS data set shows a maximum classification accuracy of 67.5%, a sensitivity of 62% and a specificity of 73%.

In this paper, we propose a methodology based on combining probabilistic analysis with visual saliency information to classify brain MR images into normal or pathological subjects. Topic regions are identified using the probabilistic analysis, and then regional saliency information is extracted to feed the classifier, which will categorize the images into their corresponding group. The rest of the paper is organized as follows: Section 2 describes the proposed method, starting with the explanation on how the features are being extracted from the MR brain images in order to group them into a cluster and organizing it with an histogram which constructs a vocabulary of visual words, information that will be used to train the PLSA method to infer hidden topics on images. Following the Saliency process will extract the region of interest of the topic maps constructed in the previous step. With the saliency images we proceed to use a classifier to categorize them into groups. Finally in section 3 the results of the proposed approach are shown.

2 PROPOSED METHOD

The main issue in the automatic diagnosis of AD (specially at early stages) using structural images is the complex alteration patterns that indicates the presence or absence of the pathology. Currently, these structural changes are analyzed at a local scale, by partitioning the brain in functional and anatomical regions (given by an atlas) and reporting the alterations per region; however, complex relations between these alterations are not studied or reported. To cope with this issue,
a two-stage analysis is proposed, by first learning image regions that captures latent information shared by the image pixels, and then extracting saliency or relevant information from each region that could be discriminant for the specific pathology.

The proposed method involves 3 different stages, depicted in Figure 1, starting from image features extracted from each brain MR volume. First, using the probabilistic Latent Semantic Analysis (pLSA) method [6], relations between feature patches are learned to identify latent topics that allows to partition each image into topics regions. Then, for each region a saliency map is calculated using the Graph-Based Visual Saliency method proposed by Harel et al. [7]. Finally, the regional saliency maps are combined into a single map, and all maps are compared with each others using a similarity measure, information which allows to classify the images into normal controls or probable AD subjects by training a Support Vector Machine classifier.

2.1 Region extraction with pLSA

The first objective is to identify topics regions in brain MR images that can be associated with presence or absence of the pathology, without introducing any prior knowledge about the disease. To extract automatically this regions, a two-step process is proposed, comprised of a learning process and an identification procedure. Starting from a set of training images, which are characterized using a multi-scale edge analysis, a clusterization algorithm is applied in the feature space to obtain a reduced set of visual primitives (visual words). Then, a pLSA model is trained to infer the latent topics associated with the brain.
regions. Finally, for the identification procedure, test images are processed using the probabilities learned with pLSA to identify latent variables which can be associated with information related to the main brain tissues. Each image patch has associated one of these latent variables, or topics, thus conforming a map of topic regions.

The feature extraction process begins by randomly sampling a set of patches from training images. These are characterized by using a multi-scale edge analysis: an edge detection operator $E_f$, implemented as 3x3 and 5x5 Sobel kernels applied in the horizontal and vertical directions. Edge information is then concatenated into a single vector, to represent each image patch as a point in a feature space. All instances in this space are grouped into a fixed number of clusters by using a conventional clustering algorithm (k-means)[8], forming a visual vocabulary. Finally, this vocabulary is used to represent each training image by a histogram of visual words.

With the training histograms we proceed to train a Probabilistic Latent Semantic Analysis (pLSA). This approach is based in the statistical latent class model, which analyses the data co-occurrences and their associations with unobservable variables. This technique helps to find relationships between hidden topics [9], by transforming geometric patterns in visual words and then set their co-occurrences as latent topics. The learned topic probabilities comprises a model that allows to predict latent topics in test images.

The statistical pLSA model in images starts by partitioning the image into patches $d_i$, describing each one as a mixture of visual words $w_j$. Then, these two variables are assumed to be conditionally independent given a set of unobservable topics $z_k$. We use a multinomial distribution $P(z|d_i)$ to model each document (patch) as a mixture of latent topics. The visual words are used to perform a description of the latent topics. The process of getting a set of observations $(w, d)$ can be described by the following probabilistic model.

$$P(d_i, w_j) = P(d_i)P(w_j|d_i), \quad P(w_j|d_i) = \sum_{l=1}^{k} P(w_j|z_l)P(z_l|d_i)$$ (1)

As the topic distribution is not an observed variable, the probability of the unobservable distributions $P(z_l|d_i)$ and $P(w_j|z_l)$ can be learned from the likelihood of the observed data

$$L = \prod_{j=1}^{N} \prod_{i=1}^{M} P(w_j|d_i)^{n(w_j|d_i)}$$ (2)

Where $N$ is the number of patches of the image, $M$ is the number of words in the visual vocabulary, $n(w_j, d_i)$ is the number of word occurrences $w_j$ in a patch $d_i$ and $P(w_j|d_i)$ is given by Equation 2.

Best model parameters are found by using the Expectation-Maximization (EM) algorithm, which estimates all the posterior probabilities for latent variables $P(z_l|d_i, w_j)$, while optimizing $P(w_j|z_l)$ and $P(z_l|d_i)$. This algorithm is implemented as an iterative process, which stops when it reach convergence.
Once the pLSA model and its probabilities are learned, the identification procedure takes place, where test MRI brain volume are labeled to identify regions given by the latent topics. Each image is partitioned into visual patches, each one containing a fixed number of image words. For each patch, the latent topic probabilities are estimated per word using the EM algorithm, but keeping fixed the conditional probability distribution \( P(w_j|z_i) \) at each iteration. With this procedure, each word is assigned to a latent topic, so that the whole image is described as a regional topic map.

### 2.2 Saliency maps with GBVS

After region identification on brain MR test image, the next step includes to extract saliency information within each region. There exists a large number of approaches to calculate salient points and saliency maps in natural images, but given the particular structure and patterns of medical images, these methods cannot be directly applied in the medical context. We have found that the Graph-Based Visual Saliency approach of Harel et al. [7] can work well on brain MR volumes, because it includes a semantic notion of dissimilarity between pixels that may emulate the method of a radiologist when analyzing the images.

GBVS combines the dissimilarity between pixels with a notion of closeness as a straight manner to calculate saliency values, by modeling the image as a fully-connected graph and storing information at edges. There are three steps to calculate the saliency maps: feature extraction, activation maps and combination. First, some relevant features, such as intensity, orientation and contrast are extracted at different scales of the original image. Then, for each feature and scale image a fully connected graph is constructed by storing the dissimilarity and closeness information at each edge. With the graphs, activation maps are estimated by constructing a Markov Chain onto the graph and calculating its equilibrium distribution as the principal eigenvector of the transition matrix. Each activation map is normalized by concentrating the mass calculated in the activation step, using the same Markovian approach. Finally, the method averages the saliency maps per features and combines them into the master saliency map. This map corresponds to a grayscale image where the more brighter, the more salient the pixel is.

### 2.3 Image classification using SVM

The Support Vector Machine is a supervised learning model, that takes a set feature information and predicts for each instance to which of the possible two classes belong. It is based on a nonlinear mapping of each element to the feature space, previously defined by a kernel function.

In our case, two different classes of MR brain images were considered (normal control (NC) and probable AD patients), and the elements to be classified corresponds to the master saliency maps of each brain MR test image. The pre-computed kernel is constructed by finding similarity between all images (in a
one-to-one comparison) using a histogram intersection. To do so, each image is individually normalized (to resembling a histogram) and then compared using

\[ H_{\text{int}}(s_p, s_q) = \sum_i \sum_j \sum_k \min \{ s_p(i, j, k), s_q(i, j, k) \} \]  

(3)

The obtained values ranges from 0 (no overlapping or intersection) to 1 (complete overlapping or intersection), giving as a result a kernel matrix which fed the SVM classifier. An initial cross validation is performed to adjust the value of the penalty parameter C, with the optimal value the final classification of test images is performed.

3 PRELIMINARY RESULTS

A set of 56 brain MR images from healthy (28) and pathological (28) subjects, extracted from the OASIS (Open Access Series of Imaging Studies) database [10], were used to preliminarily evaluate the performance of the proposed approach. Each subject has been previously analysed with a Mini-Mental State Examination (MMSE) and a Clinical Dementia Rating (CDR), and diagnosed as normal controls or with probable Alzheimer’s disease using the scores obtained in the MMSE and CDR tests. Age of the selected subjects ranges between 65 and 96 years, and pathological (AD) subjects were selected using a CDR = 1, which indicates probable mild AD. The OASIS database provides a number of images per subject, from which we have selected the skull-stripped gain-field corrected atlas-registered image to the 1988 atlas space of Talairach and Tournoux. From each volume, only one sagittal slice were selected, and then the image set was splitted into a training set (20 non-demented and 20 demented subjects) and one testing set (16 subjects).

![Fig. 2](image)

**Fig. 2.** Left, MR brain image AD patient, center, The topic map found by pLSA and with the applied GBVS method. Right, the GBVS image of the AD patient.

Classification performance was assessed by computing the accuracy rate, according to the ground truth provided with the OASIS database (defined by neurological tests). From the 16 test images, 7 normal controls and 5 Alzheimer’s
subjects were correctly classified, leading to an accuracy rate of 75%. This results are reported in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>NC</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 1. Confusion matrix for classification of 16 test brain MR images

4 CONCLUSION

In this paper we presented a strategy that helps to classify pathological brains with MR images, it is based on topic regions and saliency maps. The method was proposed, implemented and evaluated. This strategy provides a subject classification between two groups normal/control or AD patients, the analysis was previously compared with diagnosis given by experts.

Applying pLSA to the images has allowed us to infer hidden topics, which are present in the visual words and belongs to a set of image patches. The interaction between topics and brain structures can be related with the obtained information. Using Saliency maps to highlight regions in the topics has allowed us to determine what changes can occur within different regions in order to find patterns and complex relation that could be discriminant for the specific pathology.

The proposed approach was evaluated on a public brain MR image dataset (OASIS). Even though the proposed classification scheme has been tested with a small dataset, the preliminary results have shown that this approach seems to be promising for successfully classify of normal and pathological subjects, and also, for semantic extraction of relevant patterns associated with the Alzheimer’s disease. Further work includes performing an extensive validation with more brain MR images and with complete volume of MR images.
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3 Classification of Alzheimer’s disease using regional saliency maps from brain MR volumes

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Classification of Alzheimer’s Disease using Regional Saliency Maps from Brain MR volumes

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ABSTRACT

Accurate diagnosis of Alzheimer’s disease (AD) from structural Magnetic Resonance (MR) images is difficult due to the complex alteration of patterns in brain anatomy that could indicate the presence or absence of the pathology. Currently, an effective approach that allows to interpret the disease in terms of global and local changes is not available in the clinical practice. In this paper, we propose an approach for classification of brain MR images, based on finding pathology-related patterns through the identification of regional structural changes. The approach combines a probabilistic Latent Semantic Analysis (pLSA) technique, which allows to identify image regions through latent topics inferred from the brain MR slices, with a bottom-up Graph-Based Visual Saliency (GBVS) model, which calculates maps of relevant information per region. Regional saliency maps are finally combined into a single map on each slice, obtaining a master saliency map of each brain volume. The proposed approach includes a one-to-one comparison of the saliency maps which feeds a Support Vector Machine (SVM) classifier, to group test subjects into normal or probable AD subjects. A set of 156 brain MR images from healthy (76) and pathological (80) subjects, splitted into a training set (10 non-demented and 10 demented subjects) and one testing set (136 subjects), was used to evaluate the performance of the proposed approach. Preliminary results show that the proposed method reaches a maximum classification accuracy of 87.21%.

Keywords: Alzheimer’s disease, MRI, Visual Attention Models, probabilistic Latent Semantic Analysis

1. DESCRIPTION OF PURPOSE

Alzheimer’s disease (AD) is the most common type of dementia, affecting over 20 millions of people in the world. Currently, an effective technique or biomarker to detect AD in early stages is not yet available. Usually, neurological and neuropsychological information coming from the patient history, history from relatives and clinical observations is collected and analyzed to detect AD. However, this procedure allows to diagnose the disease when this is in an advanced stage, impeding any possibility for the patient to change their lifestyle and prevent the evolution of this pathology. Nowadays, neuroimaging research plays an important role in early diagnosis of AD, by extracting useful information and relations from structural (Magnetic Resonance Imaging, MRI), functional (Functional MRI, fMRI) and blood perfusion (Single-Photon Emission Computed Tomography, SPECT) data, among others. In MRI, structural changes in brain regions, such as atrophy, becomes evident during the disease progression. In particular, initial analysis of these images have shown that hippocampal atrophy is one of the first manifestations of the disease: for patients previously diagnosed with mild AD, the hippocampus area has been reduced about 15% to 25%, compared to healthy patients, showing that this atrophy may be detectable five years before symptoms.
Currently the most used techniques to extract and analyze patterns of structural changes in brain MR images associated to neurological pathologies are known as Voxel-Based Morphometry (VBM)\(^3\) and Deformation-Based Morphometry (DBM).\(^4\) In VBM, local differences in brain tissue segmentations are statistically analyzed voxel-by-voxel by normalizing each volume into a stereotactic template, while DBM analyses information coming from the deformations fields obtained after registration to the template. With these methods, one-to-one correspondences between subjects are assumed to effectively analyze the volume information, assumption that could not be true due to the intrinsic anatomical variability within subjects. Recently, Feature-Based Morphometry (FBM)\(^5\) has been proposed to cope with this issue, by extracting and identifying anatomical patterns that are statistically significant, and characterizing them as local features that replaces the global template for morphometry analyses. This approach has been tested over the OASIS data set,\(^6\) achieving a maximum classification performance of 0.80 in the Equal Error Rate measure. Another classification approach has been proposed in,\(^7\) where the brain images are decomposed into basis functions by means of an Independent Component Analysis (ICA) technique, information which fed a Support Vector Machine (SVM) classifier. Experimental results on the OASIS data set shows a maximum classification accuracy of 67.5%, a sensitivity of 62% and a specificity of 73%.

The main issue in the automatic diagnosis of AD using structural images is the complex alteration patterns that could indicate the presence or absence of the pathology. Currently, these structural changes are analyzed at a local scale, by partitioning the brain in functional and anatomical regions (given by an atlas) and reporting the alterations per region; however, complex relations between alterations are not studied or reported.

2. PROPOSED METHOD

The proposed method involves 3 different stages, depicted in Figure 1, starting with the feature extraction from each slice of each brain MR volume. Then, relations between feature patches are learned through the probabilistic Latent Semantic Analysis (pLSA),\(^8\) to identify latent topics that allows to partition each image into topic regions. Then, for each region a saliency map is calculated using the Graph-Based Visual Saliency method proposed by Harel et al.\(^9\) The regional saliency maps are then combined into a single map on each slice of the MR brain volume. Finally, all volume maps are compared using a similarity measure, information used to train a Support Vector Machine (SVM) classifier, allowing to group the volumes into normal controls or probable AD subjects.

2.1 Region extraction with pLSA

The first objective is to identify topics regions on each slice of the brain MR volume that can be associated with presence or absence of the pathology, without introducing any prior knowledge about the disease. To extract automatically these regions, a two-stage process is proposed, comprised of a learning step and an identification procedure. Starting from a set of training images, which are characterized using a multi-scale edge analysis, a set of randomly sampled image patches are extracted to obtain a reduced set of visual primitives (visual words). Then, pLSA is trained to infer latent topics associated with brain regions. Finally, for the identification procedure, test slices are processed using the probabilities learned with pLSA to identify the topics associated to each slice, thus conforming the map of topic regions.

The process begins by selecting a group of slices of each volume to extract features using a set of patches randomly sampled from training slices. Those patches are characterized by an edge detection operator, implemented as 3x3 and 5x5 Sobel kernels applied in the horizontal and vertical directions. Feature (edge) information is first concatenated into a single vector and collected together, thus forming a visual vocabulary. Finally, this vocabulary is used to represent each training slice by a histogram of visual words, suitable to train the pLSA.
This technique helps to find relationships between hidden topics, by transforming geometric patterns in visual words and then set their co-occurrences as latent topics. The learned topics will allow predicting latent topics in test slices. pLSA starts by partitioning the slices into patches $d_i$, describing each as a mixture of visual words $w_j$. Then, these two variables are assumed to be conditionally independent given a set of unobservable topics $z_k$. We use a multinomial distribution $P(z|d_i)$ to model each document as a mixture of latent topics. The visual words are used to perform a description of the latent topics. The process of getting a set of observations $(w, d)$ can be described by the following probabilistic model.

$$P(d_i, w_j) = P(d_i)P(w_j|d_i), \quad P(w_j|d_i) = \sum_{l=1}^{k} P(w_j|z_l)P(z_l|d_i), \quad (1)$$

As the topic distribution is not an observed variable, the probability of the unobservable distributions $P(z_l|d_i)$ and $P(w_j|z_l)$ can be learned from the likelihood of the observed data.

$$L = \prod_{j=1}^{N} \prod_{i=1}^{M} P(w_j|d_i)^{n(w_j|d_i)}, \quad (2)$$

Where $N$ is the number of patches of the slice, $M$ is the number of words in the visual vocabulary, $n(w_j, d_i)$ is the number of word occurrences $w_j$ in a patch $d_i$ and $P(w_j|d_i)$ is given by Equation 2. Best model parameters are found by using the Expectation-Maximization (EM) algorithm, which estimates all the posterior probabilities for latent variables $P(z_l|d, w_j)$, while optimizing $P(w_j|z_l)$ and $P(z_l|d_i)$. This algorithm is implemented as an iterative process, which stops when it achieve convergence.

Once probabilities are learned, the identification procedure takes place, where test MRI brain volumes are labeled to identify regions given by the latent topics. Each slice is partitioned into visual patches that contain
a fixed number of image words. For each document, the latent topic probabilities are estimated per word using
the EM algorithm, but keeping fixed the conditional probability distribution $P(w_j | z_i)$ at each iteration.

### 2.2 Saliency maps with GBVS

After region identification on each slice of the brain MR test volume, the next step is to extract saliency information within each region. Calculation of saliency maps on volumetric MR brain images can be performed by applying a visual attention method. There exists a large number of approaches to calculate salient points and saliency maps in natural images, but given the particular structure and patterns of medical images, these methods cannot be directly applied in the medical context. We have found that the Graph-Based Visual Saliency approach of Harel et al.\textsuperscript{9} can work well on brain MR volumes, because it includes a semantic notion of dissimilarity between pixels that may emulate the method of a radiologist when analyzing the images.\textsuperscript{10}

As saliency information relies on the relation between image features, Figure 2 shows how salient maps are constructed.

GBVS combines the dissimilarity between pixels with a notion of closeness as a straight manner to calculate saliency values, by modeling the image as a fully-connected graph and storing information at edges. There are three steps to calculate the saliency maps: feature extraction, activation maps and combination. First, some relevant features, such as intensity, orientation and contrast are extracted at different scales of the original image. Then, for each feature and scale image a fully connected graph is constructed by storing the dissimilarity and closeness information at each edge. With the graphs, activation maps are estimated by constructing a Markov Chain onto the graph and calculating its equilibrium distribution as the principal eigenvector of the transition matrix. Each activation map is normalized by concentrating the mass calculated in the activation step, using...
the same Markovian approach. Finally, the method averages the saliency maps per features and combines them into the master saliency map.

2.3 Image classification using SVM

The Support Vector Machine is a supervised learning model that takes a feature set information and predicts for each instance to which of the possible two classes belong. It is based on a nonlinear mapping of each element to the feature space, previously defined by a kernel function $k(x_i; x_j)$ which intuitively computes the similarity between samples $x_i$ and $x_j$. This kernel is a projection of the data to another space in which data can be linearly separable. The success of SVM depends on good kernels choice which are typically hand-crafted and known in advance.

In our case, two different classes of MR brain volumes were considered (normal control (NC) and probable AD patients), and the elements to be classified corresponds to the master saliency maps of each brain MR test slice. The pre-computed kernel is constructed by finding similarity between all volumes (in a one-to-one comparison) using a histogram intersection. To do so, each slice is individually normalized (to resembling a histogram) and then compared using:

$$H_{int}(s_p, s_q) = \sum_i \sum_j \sum_k \min \{s_p(i, j, k), s_q(i, j, k)\},$$  \hspace{1cm} (3)

The obtained values ranges from 0 (no overlapping or intersection) to 1 (complete overlapping or intersection), gives as a result, a kernel matrix which fed the SVM classifier. An initial cross validation is performed to adjust the value of the penalty parameter C, with the optimal value the final classification of test volume is performed.

3. PRELIMINARY RESULTS

A set of 156 brain MR volumes from healthy (80) and pathological (76) subjects, extracted from the OASIS (Open Access Series of Imaging Studies) database, were used to preliminarily evaluate the performance of the proposed approach. Each subject was analyzed with a Mini-Mental State Examination (MMSE) and a Clinical Dementia Rating (CDR), and diagnosed as normal controls or with probable Alzheimer disease using the scores obtained in the MMSE and CDR tests. Age of the selected subjects ranges between 60 and 80 years, and pathological (AD) subjects were selected using a CDR = 1 and 0.5, which indicates probable mild and very mild AD. The OASIS database provides a number of images per subject, from which we have selected the skull-stripped gain-field corrected atlas-registered image to the 1988 atlas space of Talairach and Tournoux. The data set was split into a training set 10 non-demented and 10 demented subjects. Classification results are reported on 2 different groups of test subjects, to illustrate the effect of age and severity of clinical diagnosis on classification performance:

1. Group 1: Subjects aged 60 to 80 years, mild AD (CDR=1) (66 NC, 20 AD)
2. Group 2: Subjects aged 60 to 80 years, both mild and very mild AD (CDR=1 and 0.5) (66 NC, 70 AD)

Image results are shown in Figures and respectively, which shows slices of normal and control MR brain images and the difference between the GBVS applied onto the original images, and the application of our method first using pLSA and then applying GBVS on the topic maps, giving as a result a saliency map per region.
Classification performance was assessed by computing the accuracy rate, according to the ground truth provided with the OASIS database (defined by neurological tests). From the 136 test volumes. Results are reported in Table 1. The following metrics where used to validate the method:

- Accuracy (Acc) = \( \frac{TP + TN}{TP + TN + FP + FN} \)
- Sensitivity (Sens) = \( \frac{TP}{TP + FN} \)
- Specificity (Spec) = \( \frac{TN}{FP + TN} \)
- Balanced Accuracy (BAC) = \( \frac{Sens + Spec}{2} \)
- Equal Error Rate (EER): the point on a ROC (Receiving Operating Characteristic) curve where the false positive rate and false reject rate (1 - true positive rate) are equal.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>87.21</td>
<td>69.85</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85</td>
<td>67.14</td>
</tr>
<tr>
<td>Specificity</td>
<td>87.77</td>
<td>72.73</td>
</tr>
<tr>
<td>Balanced Accuracy</td>
<td>86.44</td>
<td>69.93</td>
</tr>
</tbody>
</table>

Table 1. Classification of 136 test brain MR volumes

Our method was compared with the equal error rate FBM method,\(^5\) which presents the same groups using The OASIS Database. Group 1 is conformed by subjects aged 60 to 80 years with mild AD and Controls. While group 2 is conformed by subjects aged 60 to 80 years, both with mild and very mild AD and control. Result are shown in table 2.

4. ORIGINAL CONTRIBUTION

In this paper, we propose a methodology based on combining a probabilistic analysis with visual saliency information for classification of structural brain MR volumes into normal or pathological (AD) subjects. Latent
Table 2. Comparison of the equal error rate between Our method and FBM method

<table>
<thead>
<tr>
<th></th>
<th>Proposed Method</th>
<th>FBM od Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.86</td>
<td>0.80</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.71</td>
<td>0.71</td>
</tr>
</tbody>
</table>

regions related with the brain structure are identified using pLSA, while regional saliency information is extracted for each region using GBVS. The master saliency maps obtained allows to feed an SVM classifier, which categorizes a set of test brain MR volumes into their corresponding group with an accuracy of 87.21% for group 1 and 69.85% for group 2.

5. CONCLUSION

In this paper we proposed, implemented and evaluated a strategy that aims to classify pathological subjects from brain MR images, based on extracting regional saliency maps. The proposed approach provides a subject classification into normal controls or AD patients, analysis that was further compared with the diagnosis given by expert radiologists. Application of a statistical approach, such as pLSA, allows to infer hidden topics present in the images with respect to a visual vocabulary extracted from training images. The latent topics have shown to be strongly related with the main brain tissues. In addition, regional saliency information allows to find patterns and complex relations that could be discriminant for the specific pathology. The proposed approach was evaluated on a subset of a public brain MR image dataset (OASIS). This method was also validated against FBM method and it shows a better performance in group 1 and an equal performance in group 2. With our method regional changes can be seen. Preliminary results have shown that this approach seems to be promising for successfully classify normal and pathological subjects, and also, for semantic extraction of relevant patterns associated with the Alzheimer’s disease. Further work includes to perform an extensive validation with other brain MR image datasets that include patients suffering other AD-related pathologies such as Mild Cognitive Impairment.

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Discovering Regional Pathological Patterns in Brain MRI

As presented on the "International Workshop on Pattern Recognition in NeuroImaging“ PRNI 2013, July 2013
Discovering Regional Pathological Patterns in Brain MRI

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Abstract—The Alzheimer disease diagnosis using Brain Magnetic Resonance (MR) Imaging is a difficult task, owing to complex arrangement of patterns that may be present in a particular neurodegenerative disease. Nowadays, the diagnosis of this pathology does not take into account those patterns and using these MR images only when the disease is in an advance stage. In this paper we propose a strategy which Interpret and classify the brain structure using a framework that highlights relevant brain patterns by combining a probabilistic technique which identifies and groups regions with similar visual features with a visual saliency method, which highlights relevant patterns. A classification task was performed to evaluate the performance of this approach. A set of 156 brain MR images from healthy (76) and pathological (80) subjects, was divided into a training set of 20 subjects and a testing set of 136 subjects. Preliminary results show that the proposed method reaches a maximum classification accuracy of 81.39%

Complex pathological brain patterns generally are found in neurodegenerative diseases which can be correlated with different clinical onsets of a particular pathology. Currently, an objective method that aids to determine such signs, in terms of global and local changes, is not available in clinical practice and the whole interpretation is dependent on the radiologist’s skills. In this paper, we propose a fully automatic method that analyzes the brain structure under a multidimensional frame and highlights relevant brain patterns. An association of such patterns with the disease is herein evaluated in three classification tasks, involving probable Alzheimer’s disease (AD) patients, Mild Cognitive Impairment (MCI) patients and normal subjects (NC). A set of 75 brain MR images from NC subjects (25), MCI (25) and probable AD (25) patients, split into training (15 subjects) and testing (60 subjects) sets, was used to evaluate the performance of the proposed approach. Preliminary results show that the proposed method reaches a maximum classification accuracy of 80% when discriminating AD patients from NC, of 75% for classification of MCI patients from NC.

Keywords—Alzheimer’s disease; MRI; Visual Attention Models; probabilistic Latent Semantic Analysis

I. INTRODUCTION

Nowadays, neuroimaging research plays an important role in early diagnosis of neurodegenerative diseases, by extracting useful information and relations from structural Magnetic Resonance (MR) images. These structural changes are analyzed at a local scale, by partitioning the brain in functional and anatomical regions (given by an atlas) and reporting the alterations per region, however, complex relations between these alterations are not further studied or reported. Voxel-Based Morphometry (VBM) [1] and Deformation-Based Morphometry (DBM) [2] are the most used techniques to extract and analyze such structural patterns of change. In VBM, local differences in brain tissue segmentations are voxel-by-voxel statistically analyzed by normalizing each volume into a stereotactic template, while DBM analyses information coming from the deformations fields obtained after registration to the template. With these methods, one-to-one correspondences between subjects are assumed to effectively analyze the volume information, a weak assumption that neglects the intrinsic within-subject anatomical variability. Recently, Feature-Based Morphometry (FBM) [3] has been proposed to cope with this issue, by extracting and identifying anatomical patterns that are statistically significant, and characterizing them as local features that replaces the global template for morphometry analyses.

Alzheimer’s disease is the most common type of dementia (one type of neurodegenerative diseases), affecting over 20 millions of people in the world. In the clinical practice, neurological and neuropsychological information coming from the patient, history from relatives and clinical observations is collected and analyzed to detect the probability of AD. If most of these criteria are not met for AD, but cognitive impairment is still present, the patient can be diagnosed with MCI [4], considered a transitional period between normal aging and probable AD. Currently, an objective and accurate technique, to detect a probable AD in early stages and to predict the possible conversion of MCI patients to AD, is not yet available, delaying any possibility for the patients to change their lifestyle.

A main concern towards an automatic diagnosis of neurodegenerative diseases, using structural images, is the complex arrangement of anatomical patterns that could indicate the presence or absence of the pathology. In this paper, we propose a novel method that seeks complex associations of anatomical features, by combining a probabilistic analysis which groups up common visual brain features, with a visual
saliency method, which extracts relevant information using a multiresolution framework by following what radiologists do when they analyze visual patterns in medical images. The obtained regional saliency maps, besides of being useful for classification of brain MR images, allows setting a relevance pathological value to any of the previously segmented anatomical brain regions. This approach achieves a quantitative discrimination of brain anatomical regions, associated or not to the presence of probable AD or MCI.

II. PROPOSED METHOD

The aim of the proposed approach is to highlight patterns in regions with similar visual features, even though they are not connected. The whole method is illustrated in Figure 1. First, a global low-level feature is extracted in a slice-by-slice basis from the input brain MR volumes, searching to improve the image sparsity. Then, the obtained image is split and a set of randomly selected patches is collected. The probabilistic Latent Semantic Analysis (pLSA) [5] softly clusterizes these data, identifying latent topics related with common visual features. Patterns within each region are revealed by means of a saliency map calculated from a Graph-Based Visual Saliency method [6]. The obtained regional saliency maps are then mixed together into a single map which is normalized. The histogram intersection can be used as a kernel function. Afterwards, a Support Vector Machine (SVM) classifier assigns to each volume a relevance pathological value to any of the previously segmented anatomical brain regions. This approach achieves a quantitative discrimination of brain anatomical regions, associated or not to the presence of probable AD or MCI.

A. Brain Region Extraction

A first objective is to identify common visual features on brain MR slices that can be associated with the presence or absence of the pathology, without introducing any prior knowledge about the disease. These regions are automatically determined with a probabilistic learning procedure applied on a set of training images, which are characterized using orientation information since only subtle global changes are searched. A set of randomly sampled image patches are then extracted to obtain a reduced set of visual primitives (visual words) and the probabilistic approach (pLSA) is trained to infer latent topics associated with common visual features. Finally, a set of test images are processed using the probabilities learned with pLSA.

The process begins by manually selecting a group of 4 slices of each training volume and by extracting orientation information from them, using a set of Gabor filters. As a result, four orientation volumes, calculated with 0°, 45°, 90° and 135° Gabor filters, are obtained from each volume. Then, a visual vocabulary (3000 patches) is constructed by randomly selecting image positions, extracting patches (size 3 × 3 pixels) from the four orientation images at each position and concatenating the orientation information into a single vector by position. Finally, this vocabulary is used to represent each training slice as a histogram of visual words.

The probabilistic analysis starts by partitioning the slices into a set of overcomplete documents \( d_i \) (size 18 × 18 pixels with overlay of 9 pixels) and describing each as a mixture of latent topics and the visual words are used to perform a description of the latent topics. The joint probability of \( (w, d) \) can be described as:

\[
P(d_i, w_j) = P(d_i) P(w_j|d_i)
\]

\[
P(w_j|d_i) = \sum_{l=1}^{k} P(w_j|z_l) P(z_l|d_i)
\]

As the topic distribution is not an observed variable, the probability of the unobservable distributions \( P(z_l|d_i) \) and \( P(w_j|z_l) \) can be learned from the likelihood of the observed data:

\[
L = \prod_{j=1}^{N} \prod_{i=1}^{M} P(w_j|d_i)^{n(w_j|d_i)},
\]

where \( N \) is the number of documents in the slice, \( M \) is the number of words in the visual vocabulary, \( n(w_j, d_i) \) is the number of word occurrences \( w_j \) in a document \( d_i \) and \( P(w_j|d_i) \) is given by Equation 1. Best model parameters are found by using the Expectation-Maximization (EM) algorithm, which estimates all the posterior probabilities for the latent variables \( P(z_l|d_i, w_j) \), while optimizing \( P(w_j|z_l) \) and \( P(z_l|d_i) \). This algorithm is implemented as an iterative process, which stops when it reaches convergence.

Once the probabilities are learned, the identification procedure takes place, where a set of test MRI brain volumes are labeled to identify regions given by the latent topics. Each volume’s slice is partitioned into a set of documents, containing a fixed number of image words. For each document, the latent topic probabilities are estimated using the...
EM algorithm, but keeping fixed the conditional probability distribution $P(w_j|z_i)$ at each iteration.

B. Regional Saliency Maps

After region identification on each slice of the brain MR test volume, the next step is to extract relevant visual information within each region. A Graph-Based Visual Saliency approach [6] has been herein applied, particularly because it includes a semantic notion of dissimilarity between pixels that may emulate what a radiologist does when examining cases.

GBVS combines the dissimilarity between pixels with a notion of closeness to calculate saliency values and models the image as a fully-connected graph. There are three steps to calculate the saliency maps: feature extraction, activation maps and combination, as depicted in Figure 2. First, relevant features, namely intensity, orientation and Sobel edges, are extracted at different scales. Then, for each feature and scale, a fully-connected graph is constructed by using the image pixels as nodes and the dissimilarity and closeness information as the edge weights. With the graphs, activation maps are estimated by constructing a Markov Chain onto each graph and calculating its equilibrium distribution as the principal eigenvector of the transition matrix of the graph. Each activation map is further normalized by concentrating the mass calculated in the activation step, using the same Markovian approach. Finally, the method averages the saliency maps per feature and combines them into the final master saliency map.

Given the regional partition obtained from the probabilistic approach, each of these regions is used for masking the original brain volume and an individual master saliency map is calculated independently. Finally, the individual maps are combined into one single volume, thus conforming the regional saliency map of the brain volume.

C. Image Classification

The Support Vector Machine (SVM) is a supervised learning model that takes a feature information set and predicts for each instance to which of two possible classes it belongs. It is based on a nonlinear mapping of each element to the feature space, defined by a kernel function $k(x_i; x_j)$, which intuitively computes the similarity between samples $x_i$ and $x_j$. This kernel acts then as a projection of the elements to another space, in which data can be linearly separable. The success of SVM depends on a good kernel choice, which are typically hand-crafted and known in advance.

In this case, three different classes of MR brain volumes were considered (normal controls (NC), MCI patients (MCI) and probable AD patients (AD)). As the SVM approach only allows binary classifications, three different classification experiments were performed: discrimination of AD from NC, and discrimination of MCI from NC. The elements to be classified corresponds to the master saliency maps of each brain MR test volume. The pre-computed kernel is constructed by calculating similarity scores between all regional saliency maps (in a one-to-one comparison) using a histogram intersection. To do so, each volume is individually normalized (obtaining a histogram) and then compared using:

$$\mathcal{H}_{int}(s_p, s_q) = \sum_i \sum_j \sum_k \min\{s_p(i, j, k), s_q(i, j, k)\}$$

The obtained values ranges from 0 (no overlapping or intersection) to 1 (complete overlapping or intersection), giving as a result a kernel matrix which feeds the SVM classifier.

An initial cross validation is performed to adjust the value of the penalty parameter C, and with the optimal value, the final classification of the test volumes is performed.

D. Anatomical Interpretation

To highlight anatomical areas related with a particular pathology, the proposed approach estimates quantitatively brain differences using the regional saliency maps and the predefined kernel of the SVM. The values that define the separating hyperplane, allow to identify the most relevant regions for AD or MCI discrimination from the NC class, by using the coefficient value assigned to each regional saliency map (positive values for the pathology and negative values for the normal class). Those relevant regions can be visualized in an overall discrimination relevance map by performing a linear combination of the regional saliency maps and their corresponding coefficients. To better identify the relevant regions and correlate them with anatomical locations, 96 cortical and 21 subcortical structural areas obtained from the Harvard-Oxford atlas [7] have been used to label the Regions of Interest. For each anatomical region, the mean value of the discrimination relevance map is stored, allowing to set different disease patterns at quantifying the importance of each anatomical area.

III. Preliminary Results

A set of 75 brain MR volumes from healthy (25), MCI (25) and AD (25) subjects, acquired in a 3T GE Signa II scanner at the Alzheimer’s Research Center of Fundación Reina Sofía in Madrid, were used to preliminarily evaluate
the performance of the proposed approach. Ages of selected subjects range between 65 and 88 years. The set of images were skull-stripped and atlas-registered to the 1988 atlas space of Talairach and Tournoux with BET (Brain Extraction Tool) and FLIRT (FSL Linear Image Registration Tool), included in the FMRIB Software Library (FSL) [8]. The data set was split into a training set with 5 subject from each class (15 subjects in total) and a testing set with the remaining 60 subjects. Classification results are reported on 2 different groups of test subjects, to illustrate the effect of the pathologies over the brain:

1) Group 1: Subjects aged 65 to 88 years, normal controls and probable AD patients (20 NC, 20 AD)

2) Group 2: Subjects aged 65 to 87 years, normal controls and MCI patients (20 NC, 20 MCI)

Classification performance was assessed by computing the accuracy rate, according to the ground truth provided with the data set (defined by neurological tests). The classification metrics include: accuracy (Acc), sensitivity (Sens), specificity (Spec), balanced accuracy (BAC), area under ROC curve (AUC) and equal error rate (EER).

<table>
<thead>
<tr>
<th></th>
<th>Acc</th>
<th>Sens</th>
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<th>BAC</th>
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Table I
CLASSIFICATION OF 60 TEST BRAIN MR VOLUMES

From the measures presented, it can be seen that the classification performance is better in the Group 1, this can be attributed to the fact that atrophy patterns on AD patients are more pronounced that the brain structural changes present in MCI patients. The classification performance was also tested for discrimination of MCI from AD patients, however, the obtained results were not good enough: accuracy of 57.5%, sensitivity of 57.89%, specificity of 60% and a balanced accuracy of 57.5%.

In terms of the anatomical analysis, carried out as described in Section II-D, Figures III and III present the discrimination relevance maps obtained after classification of probable AD patients versus NC and MCI patients versus NC, respectively. In these maps, those areas likely related with the presence of the pathology (AD or MCI) are drawn in red, while the areas most relevant for discrimination of normal controls are colored in blue, all of them overlaid upon a structural brain MR image.

By aligning each of the relevance maps to the Harvard-Oxford cortical and subcortical atlases, the discrimination values per region can be better identified. Discrimination of probable AD patients was mainly due to specific anatomical regions, namely the frontal orbital cortex (left and right), the anterior division of the parahippocampal gyrus (entorhinal cortex, left and right), the left subcallosal cortex, and the left thalamus, caudate and putamen. In both classification experiments, the anatomical regions systematically unchanged in the group of normal subjects were the posterior division of the right middle temporal gyrus, the anterior and posterior divisions of the right superior temporal gyrus and the left and right lateral ventricles. This anatomical analysis has been found to remarkably agree with the very known anatomical findings of MCI and AD development described in the recent literature [4].

IV. CONCLUSION

In this paper we proposed, implemented and evaluated a novel strategy that aims both to find discriminant patterns and to classify probable AD and MCI subjects from brain MR images. It is based on the combination of a soft-clustering strategy, that extracts brain regions according with specific visual features, together with a visual saliency approach, useful to identify relevant information within each region. Preliminary results suggest that this approach seems to be promising for successful classifications of normal, AD...
and MCI subjects, and also for semantic extraction of relevant patterns associated to the presence of neurodegenerative diseases. Further work includes performing an extensive validation with other brain MR image datasets.

ACKNOWLEDGMENT

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5 Extracting Regional Brain Patterns for Classification of Neurodegenerative Diseases

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Extracting Regional Brain Patterns for Classification of Neurodegenerative Diseases

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ABSTRACT

In structural Magnetic Resonance Imaging (MRI), neurodegenerative diseases generally present complex brain patterns that can be correlated with different clinical onsets. An objective method that aims to determine both global and local changes is not usually available in the clinical practice, thus the interpretation of such images is strongly dependent on the radiologist’s skills. In this paper, we propose a strategy which interprets the brain structure using a framework that highlights discriminative brain patterns for neurodegenerative diseases. This is accomplished by combining a probabilistic learning technique, which identifies and groups regions with similar visual features, with a visual saliency method that exposes relevant information within each region. The association of such patterns with a specific disease is herein evaluated in a classification task, using a dataset including 80 Alzheimer’s disease (AD) patients and 76 healthy subjects (NC). Preliminary results show that the proposed method reaches a maximum classification accuracy of 81.39%.

Keywords: Magnetic Resonance Imaging, Visual Attention Models, probabilistic Latent Semantic Analysis, Alzheimer’s disease

1. INTRODUCTION

Nowadays, neuroimaging research plays an important role in the early diagnosis of neurodegenerative diseases, by extracting useful information and relations from structural Magnetic Resonance (MR) images. These structural changes are analyzed at a local scale, by associating functional and anatomical regions (given by an atlas) and reporting alterations per region. However, complex altered patterns are not further studied or reported. Voxel-Based Morphometry (VBM)\textsuperscript{1} and Deformation-Based Morphometry (DBM)\textsuperscript{2} are the most used techniques to extract and analyze such structural patterns of change. In VBM, local differences in brain tissue segmentations are voxel-by-voxel statistically analyzed by normalizing each volume into a stereotactic template, while DBM analyses information coming from the deformations fields obtained after registration to a template. With these methods, one-to-one correspondences between subjects are assumed to effectively analyze the volume information, a weak assumption that neglects the intrinsic within-subject anatomical variability. Recently, Feature-Based Morphometry (FBM)\textsuperscript{3} has been proposed to cope with this issue, extracting and identifying anatomical patterns that are statistically significant, and characterizing them as local features that replaces the global template for morphometry analyses.

Alzheimer’s disease (AD) is the most common type of dementia (one type of neurodegenerative diseases), affecting over 20 millions of people worldwide. In the clinical practice, neurological and neuropsychological patient information, history from relatives and clinical observations are collected and analyzed to detect the probability of AD. Currently, an objective and accurate technique to detect a probable AD in early stages is not yet fully available, delaying any possibility for the patients to change their lifestyle. A main concern towards an automatic diagnosis of neurodegenerative diseases, using structural images, is the complex arrangement of anatomical patterns that could indicate the presence or absence of the pathology.

In this paper, we propose a fully-automatic method that seeks complex associations of anatomical features, by combining a probabilistic analysis which groups up common visual brain features, with a visual saliency method, which extracts relevant information using a multiresolution framework that aims to approach what radiologists do...
when they examine medical images. The obtained regional saliency maps, besides of being useful for classification of brain MR images, allow setting a relevance pathological value to any of the previously segmented anatomical brain regions. This approach achieves a quantitative discrimination of brain anatomical regions, associated or not to the presence of probable AD.

In the next section we first describe our methods, followed by experiments using the OASIS dataset. We also compare the results with other previously proposed methods.

2. PROPOSED METHOD

At analyzing structural brain MR images, a main aim is to find anatomical changes, either local or global, related to functional disturbances. Nevertheless, most methods used to compare brains establish local rather than regional differences, making the analysis prone to easily miss subtle patterns or the atypical disease entities. To cope with this issue, a two-stage analysis is proposed, by first learning image regions that share particular feature information, and then extracting relevant information from each region that could be discriminant for the specific pathology.

The proposed method, illustrated in Figure 1, follows the proposals in and involves four different stages. First, low-level features are extracted from each slice of the brain MR volumes, attempting to improve the image sparsity where only a small amount of visual features are used in each image patch. Then, a set of randomly sampled image patches are collected, forming a visual vocabulary, suitable to describe each volume as a histogram of visual words. This description is used within a probabilistic Latent Semantic Analysis (pLSA) approach, which attempts to find the underlying structure of the information, producing a set of semantic regions composed of common visual features. The third step involves the application of a visual attention model, the Graph-Based Visual Saliency approach of Harel et al., that identifies the relevant visual information within each region. Finally, a Support Vector Machine classifier is trained, using a pre-calculated similarity kernel, in order to find both the separating hyperplane between the pathological and normal classes as well as the anatomical regions relevant for the classification.

![Figure 1. Step-by-step description of the proposed method.](image)

2.1 Feature Extraction

The first objective is to characterize the brain volumes in terms of visual features, aiming to automatically identify regions that share common feature information. Starting from a set of training images, where only 4 predefined slices are selected from each volume, the structural information is characterized using a bank of Gabor filters, in four different directions: 0, 45, 90 and 135. Then, a set of 3000 image patches (size $3 \times 3$ pixels) are randomly sampled from the orientation images, concatenating into a single vector the orientation information of each random position. These image patches constitutes the visual vocabulary, used to represent each training volume by a histogram of visual words.

2.2 Brain Region Extraction

The second step starts by partitioning all training volumes into a set of overcomplete documents $d_i$ (size $18 \times 18$ pixels, 9 pixels overlap) and describing each as a mixture (histogram) of visual words. The probabilistic Latent
Semantic Analysis (pLSA) approach\(^7\) allows to identify latent (hidden) variables or topics \(z_k\) (fixed to \(k = 3\)) which acts as semantic links between the \(d_i\) documents and the \(w_j\) visual words. Given the histograms, each document is modeled as a mixture of latent topics using a multinomial distribution \(P(z|d_i)\), while the visual words are used to perform a description of the latent topics. The joint probability of \((w, d)\) can be described as:

\[
P(d_i, w_j) = P(d_i)P(w_j|d_i), \quad P(w_j|d_i) = \sum_{l=1}^{k} P(w_j|z_l)P(z_l|d_i),
\]

As the topic distribution is not an observed variable, the probability of the unobservable distributions \(P(z_l|d_i)\) and \(P(w_j|z_l)\) can be learned from the likelihood of the observed data:

\[
L = \prod_{j=1}^{N} \prod_{i=1}^{M} P(w_j|d_i)^{n(w_j|d_i)},
\]

where \(N\) is the number of documents in the slice, \(M\) is the number of words in the visual vocabulary, \(n(w_j, d_i)\) is the number of word occurrences \(w_j\) in a document \(d_i\) and \(P(w_j|d_i)\) is given by Equation 1. Best model parameters are found by using the Expectation-Maximization (EM) algorithm, which estimates all the posterior probabilities for the latent variables \(P(z_l|d, w_j)\), while optimizing \(P(w_j|z_l)\) and \(P(z_l|d_i)\). This algorithm is implemented as an iterative process, which stops when it reaches convergence.

Once the probabilities are learned, the identification procedure of the regions takes place, where the visual words of test volumes are labeled to determine their corresponding latent topic. Every slice in the volumes is partitioned into a set of visual documents (size \(18 \times 18\) pixels, 9 pixels overlap), each containing a fixed number of image words. For each document, the latent topic probabilities, from the observed words, are estimated using a partial version of the EM algorithm described previously, but keeping fixed (without updating) the conditional probability distribution \(P(w_j|z_l)\) at each iteration.

### 2.3 Regional Saliency Maps

Given the regional partition obtained from the probabilistic approach, each region is used to mask the original brain volume, in order to obtain the structural intensity information per region. Then, relevant visual information within each region need to be extracted, applying a visual attention model known as Graph-Based Visual Saliency (GBVS).\(^3\) This method attempts to emulate the method of a radiologist when analyzing medical images, by including a semantic notion of dissimilarity between image pixels, allowing to model relative changes with respect to other regions in the same image in an intuitive manner.

The GBVS method include three steps to calculate a saliency map: feature extraction, activation maps and combination. For MR images, selected features comprises intensity, orientation and Sobel edges, extracted at different scales as depicted in Figure 2. Subsequently, a fully-connected graph is defined on each feature map, where edges store information of dissimilarity between nodes (image pixels) plus their closeness (modeled using a Gaussian function). Then, activation maps are estimated by constructing a Markov Chain onto the graph and calculating its equilibrium distribution as the principal eigenvector of the transition matrix of the graph. The same Markovian approach is applied again onto each activation map to normalize them, concentrating the found activations in only few image locations. Finally, the normalized activation maps are first averaged per feature channel and then combined together into a single master saliency map.

With the structural intensity information extracted per region, an individual master saliency map is calculated independently. Finally, the individual maps are combined into one single volume, thus conforming the regional saliency map of the brain volume, as illustrated in Figure 3.

### 2.4 Classification and Anatomical Interpretation

The last step of the proposed method involves a machine learning analysis, through the use of a Support Vector Machine (SVM), able to classify the pathological and normal subjects and also to identify the anatomical regions relevant for classification. In our approach, the two classes corresponds to AD (Alzheimer’s disease) or NC.
normal control), and the elements to be classified are the regional saliency maps of each test subject calculated in the previous step. As the SVM approach requires a kernel function, which acts as a nonlinear mapping from the input space to the feature (separable) space, a similarity measure is used here to precompute the kernel. To do so, the regional saliency maps are first individually normalized (to resemble a histogram) and then compared (in a one-to-one fashion) using the histogram intersection:

\[ H_{\text{int}}(A, B) = \sum_i \sum_j \min\{A(i, j), B(i, j)\} \] (3)

The obtained values range from 0 (no overlapping or intersection) to 1 (complete overlapping or intersection), giving as a result a kernel matrix which feeds the SVM classifier. An initial cross validation is performed to adjust the value of the penalty parameter C, and with the optimal value, the final classification of the test volumes is performed.

With the learned classifier, a quantitative estimate of the brain differences can be found. The weights of the support vectors that define the separating hyperplane, allows to identify the most relevant regions for pathological discrimination, by using their coefficient values (positive for normal controls and negative for pathological
subjects). Those regions can be visualized in an overall discrimination relevance map by performing a linear combination of the regional saliency maps and their corresponding coefficients, encoding with different colors the positive (normal) and negative (pathological) contributions. Finally, to correlate those regions with anatomical areas, the Harvard-Oxford atlas\textsuperscript{9} was used to label the regions of interest with 96 cortical and 21 subcortical structural areas. For each anatomical region, the mean value of the discrimination relevance map is stored, allowing to quantify the importance of each anatomical area.

3. PRELIMINARY RESULTS

A set of 156 brain MR volumes from healthy (76) and pathological (80) subjects, extracted from the OASIS (Open Access Series of Imaging Studies) database,\textsuperscript{4} were used to preliminarily evaluate the performance of the proposed approach. Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE) scores were provided for each subject, and used to classify them as normal controls (NC) or with probable Alzheimer’s disease (AD). Per each subject, a structural MR image, previously skull-stripped, gain-field corrected and registered to the 1988 atlas space of Talairach and Tournoux, was used. The dataset was divided into a training set with 10 NC and 10 AD volumes for training the pLSA, and a test set with the remaining 66 NC and 70 AD subjects used in the subsequent steps. For comparison with previous approaches,\textsuperscript{3,5} the test set includes two different groups:

1. **Group 1**: 86 subjects, aged between 60 to 80 years, includes 66 healthy controls and 20 patients suffering only mild AD (CDR=1)

2. **Group 2**: 136 subjects, aged between 60 to 80 years, includes 66 healthy controls and 70 patients suffering both very mild and mild AD (CDR={0.5,1})

Classification at each group is performed in a leave-one-out manner, where one subject at a time is left apart and then classified using the SVM model trained on the remaining subjects. Classification performance was assessed by computing the accuracy rate, according to the ground truth provided with the OASIS database (defined by neurological tests), using the following metrics:

- **Accuracy (Acc)**: $\frac{TP + TN}{TP + TN + FP + FN}$
- **Sensitivity (Sens)**: $\frac{TP}{TP + FN}$
- **Specificity (Spec)**: $\frac{TN}{FP + TN}$
- **Balanced Accuracy (BAC)**: $\frac{Sens + Spec}{2}$
- **Equal Error Rate (EER)**: the point on a ROC (Receiving Operating Characteristic) curve where the false positive rate and false reject rate (1- true positive rate) are equal.

where TP represents the true positives, FP the false positives, TN the true negatives and FN the false negatives obtained in classification, assuming AD subjects as the positive class and NC subjects as the negative class.

The obtained results are reported in Tables 1 and 2. In the first one, the proposed approach is compared in terms of classification performance with a previous proposal that uses Sobel edge information instead of a bank of Gabor filters for training the pLSA approach. The second table includes also a comparison with the state-of-the-art FBM method, in terms of the EER measure.

From the measures presented, it can be seen that the classification performance is better in the Group 1, this can be attributed to the fact that atrophy patterns on mild AD patients are visually stronger than when very mild AD subjects are included. In terms of the feature information used for the probabilistic learning step, the Sobel-based method has a better performance in the Group 1, while the proposed approach, the Gabor-based method, performs better in the Group 2. This behavior can be explained taking into account that Sobel edges highlights global changes, while the bank of Gabor filters could explain more easily localized changes.
In terms of the anatomical analysis, Figures 4 and 5 present the discrimination relevance maps obtained after classification of probable AD patients versus NC in Groups 1 and 2, respectively. In these maps, those areas likely related with the presence of AD are drawn in red, while the areas most relevant for discrimination of normal controls are colored in blue, all of them overlaid upon a structural brain MR image. Also, by aligning each of the relevance maps to the Harvard-Oxford cortical and subcortical atlases, the specific anatomical regions related with the presence of AD can be better identified. With this analysis, the regions found as strongly related with the AD include the left and right frontal orbital cortex, the occipital fusiform cortex, the anterior and posterior divisions of the parahippocampal gyrus (entorhinal cortex), the temporal gyrus, the thalamus and the hippocampus, among others. On the other hand, the regions associated with normal subjects include the right lateral ventricle, the right putamen and the anterior division of the temporal gyrus. This anatomical analysis has been found to remarkably agree with the very known clinical findings of AD.

Figure 4. Anatomical patterns for Group 1: (a) discrimination relevance maps, (b) mean relevance values in cortical regions, (c) mean relevance values in subcortical regions.

4. CONCLUSION

In this paper we proposed, implemented and evaluated a fully-automatic strategy that aims to find discriminant patterns and to classify pathological subjects from brain MR images. It is based on the combination of a soft-clustering strategy together with a visual saliency approach, useful to identify regional relevant information, interpretable in both anatomical and pathological terms. The soft-clustering approach, based on a probabilistic learning (pLSA), allows to infer latent regions with respect to a visual vocabulary extracted with a bank of Gabor filters. In addition, regional saliency information allows to find patterns and complex relations that could be discriminant for the specific pathology. The proposed approach was evaluated on a subset of a public brain MR image dataset (OASIS), and compared to a state-of-the-art method (FBM\(^3\)). Preliminary results have shown that this approach seems to be promising for successfully classify normal and pathological subjects, and
Figure 5. Anatomical patterns for Group 2: (a) discrimination relevance maps, (b) mean relevance values in cortical regions, (c) mean relevance values in subcortical regions.

also, for semantic extraction of relevant patterns associated with the Alzheimer’s disease. Further work includes to perform an extensive validation with other brain MR image datasets that include patients suffering other AD-related pathologies such as Mild Cognitive Impairment.

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6 Conclusions and future work

This thesis presented a fully-automatic strategy that combined mathematical, statistical and computational tools that aims to extract relevant information using brain MRI to improve the interpretation of morphometric changes in the brain. The main goal of this work was to find discriminant patterns between Normal and pathological subjects, these patterns can not be easily analyzed by an expert since they are complex and distributed over the brain. Some alterations where preliminary found in a complex disease such is “Alzheimer’s disease” furthermore, this method could aim to find alterations patterns in other neuro-degenerative disease as shown in the paper entitled "Discovering Regional Pathological Patterns in Brain MRI”. The tools introduced in this thesis open a another way to analyze these images.

The soft clustering approach was helpful to find relations between visual structures not necessarily by spatial location but with the most visually similar patches among the brain volume. the visual attention methods aim to discover the most salient areas where the information is stored, the machine learning technique was helpful to validate the proposed approach. The clinical interpretability aims to identify and infer pathology-related patterns for discrimination of neurological diseases.

This thesis has opened up new research avenues by confirming that the computational analysis can be a valuable tool for understanding complex morphological differences and used to quantify and determine trends or complex patterns in anatomical structures. Future work includes the development of much more formal strategies that allow the identification of relevant information from anatomical structures useful for diagnosis, prognosis and follow-up of some diseases, a domain known as computational anatomy.
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