



Functional brain image classification using association rules defined over discriminant regions[☆]

R. Chaves^{*}, J. Ramírez, J.M. Górriz, I.A. Illán for the Alzheimer's Disease Neuroimaging Initiative

Dept. Signal Theory, Networking and Communication, University of Granada, ETSIT, 18071, Granada, Spain

ARTICLE INFO

Article history:

Received 21 April 2010

Available online 3 May 2012

Communicated by S. Sarkar

Keywords:

Functional brain imaging
Alzheimer's Disease
Fisher Discriminant Ratio
Association rules

ABSTRACT

This letter shows a novel computer aided diagnosis (CAD) system for the early diagnosis of Alzheimer's Disease (AD). The proposed method evaluates the reliability of association rules (ARs) aiming to discover interesting associations between attributes in functional brain imaging, i.e. single photon emission computed tomography (SPECT) and positron emission tomography (PET). AR mining firstly requires a masking process for reducing the computational cost, which is based on Fisher discriminant ratio (FDR), in order to identify "transactions" or relationships among discriminant brain areas. Once the activation map is achieved by means of activation estimation (AE), the resulting regions of interest (ROIs) are subjected to AR discovery with a specified minimum support and confidence. Finally, the proposed CAD system performs image classification by evaluating the number of previously mined rules from controls that are verified by each subject. Several experiments were carried out on two different image modalities (SPECT and PET) in order to highlight the generalization ability of the proposed method. The AR-based method yields an accuracy up to 92.78% (with 87.5% sensitivity and 100% specificity) and 91.33% (with 82.67% sensitivity and 100% specificity) for SPECT and PET, respectively, thus outperforming recently developed methods for early diagnosis of AD.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

Dementia, one of the most severe and frequent neurodegenerative disorders in the elderly population, has important and dramatic health as well as socio-economic implications. Furthermore, the incidence and prevalence of these diseases is increasing due to the aging population, particularly in the United States, Europe, and Japan. To date there is no single test or biomarker that can predict whether a particular person will develop the disease. With the advent of several effective treatments of AD symptoms, current consensus statements have emphasized the need for early recognition (Ramírez et al., 2009). Neuroimaging technology is advancing at an impressive pace and is having huge fallouts both at the research and at the practical clinical level. At the research level, structural and functional neuroimaging are the unique methodologies allowing the in vivo study of brain pathology at macro and micromolecular level. Functional brain imaging techniques

including single photon emission computed tomography (SPECT) and positron emission tomography (PET) provide functional information, i.e. cerebral sanguineous irrigation or metabolic activity, and enable identifying pathologic anomalies in internal tissues or organs, before anatomical and structural alterations are observable.

SPECT is a noninvasive, 3-D functional imaging modality that can be used to analyze the regional cerebral blood flow (rCBF) in subjects. A SPECT rCBF study is frequently used as a complimentary AD diagnostic tool in addition to the clinical findings. On the other hand, PET measures the rate of glucose metabolism with the tracer [¹⁸F] Fluorodeoxyglucose. In AD, characteristic brain regions show decreased glucose metabolism, specifically bilaterally regions in the temporal and parietal lobes, posterior cingulate gyri and precuneus, as well as frontal cortex and whole brain in more severely affected patients (Álvarez et al., 2011).

Conventional evaluation of functional images through visual assessments performed by experts Braak and Braak (1997) is subjective and often relies on manual reorientation, visual reading of tomographic slices and semiquantitative analysis of certain regions of interest (ROIs). Recently, a new branch of emerging research has demonstrated that machine learning techniques may also be powerful analysis tools of brain imaging, with recent works adapting state-of-the-art computer vision techniques to magnetic resonance imaging (MRI) for early AD diagnosis (Gidskehaug et al., 2008), or supervised image classification for SPECT analysis (Chaves et al., 2009, 2011).

[☆] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

^{*} Corresponding author.

E-mail address: rosach@ugr.es (R. Chaves).

Association rules (ARs) have drawn researcher's attention in the past (Agrawal and Srikant, 1994) and are typically used in market basket analysis, cross-marketing, catalog design, loss-leader analysis, store layout and customer buying pattern. The application of ARs is still a research challenge in medical imaging. For content-based retrieval, association rules are employed to reduce the dimensionality of the feature vectors that represent the images and to improve the precision of the similarity queries (Ribeiro et al., 2009). ARs have also been used for reducing the dimension of erythemato-squamous diseases dataset (Karabatak and Cevdet Ince, 2009) while classification is performed with a neural network model.

This paper shows the design of a computer aided diagnosis (CAD) system to detect early AD by means of AR mining (Agrawal and Srikant, 1994) over discriminant regions. Each subject is represented by a feature vector consisting of activated ROIs which are selected using Fisher discriminant ratio (FDR) and a threshold-based activation estimation (AE) method, similar to the one used in Turkeltaub et al. (2002). The paper is organized as follows. Section 2 describes the SPECT and PET image databases that are used to evaluate the proposed methods. The AR-based CAD system is presented in Section 3 including the procedure for ROI selection, activation estimation and AR mining. Then, this method is applied to AD detection in Section 4. The evaluation experiments are shown and discussed in Section 5, and finally conclusions are drawn in Section 6.

2. Functional brain image databases

2.1. SPECT Database

Each subject is injected with a gamma emitting technetium-99 m labeled ethyl cysteinate dimer (^{99m}Tc -ECD) radiopharmaceutical and the SPECT scan is acquired by means of a 3-head gamma camera Picker Prism 3000. Brain perfusion images are reconstructed from projection data using the filtered backprojection (FBP) in combination with a Butterworth noise filter. On the other hand, SPECT images require spatial normalization (Salas-Gonzalez et al., 2008) in order to ensure that a given voxel in different images refer to the same anatomical position. This process was done by using Statistical Parametric Mapping (SPM) (Friston et al., 2007) yielding $69 \times 95 \times 79$ normalized SPECT images. Finally, intensity level is normalized to the maximum intensity as in López et al. (2009). The images were initially labeled by experienced clinicians of the Virgen de las Nieves Hospital (Granada, Spain) as normal (NOR) for subjects without any symptoms of the disease and AD to refer to possible (AD1), probable (AD2) or certain (AD3) AD patients. In total, the database consists of 97 patients: 42 NOR and 55 AD (30 AD1, 21 AD2 and 4 AD3 depending on the stage of the disease). AD3 is the most severe state of the disease corresponding with a higher reliability in the clinician's diagnosis. Our goal is the early diagnosis of AD, that is extracting the most relevant ROIs in detection of possible AD as shown in Nestor et al. (2004). The SPECT image database used in this paper provides a suitable framework for this statistical analysis since the proportion of scans corresponding to patients in the early stage of AD is considerable, although we perform it to all labeled patients. Furthermore, this kind of classification task performs well, as we obtain a high accuracy, specificity and sensitivity as shown in the experimental section.

2.2. ^{18}F FDG PET ADNI Database

Data used in the preparation of this article were obtained from the ADNI Laboratory on NeuroImaging (LONI, University of California,

Los Angeles) website (<http://www.loni.ucla.edu/ADNI/>). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a 60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55–90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years. For up-to-date information, see <http://www.adni-info.org>.

FDG PET scans were acquired according to a standardized protocol. A 30-min dynamic emission scan, consisting of six 5-min frames, was acquired starting 30 min after the intravenous injection of 5.0 ± 0.5 mCi of ^{18}F -FDG, as the subjects, who were instructed to fast for at least 4 h prior to the scan, lay quietly in a dimly lit room with their eyes open and minimal sensory stimulation. Data were corrected for radiation-attenuation and scatter using transmission scans from Ge-68 rotating rod sources and reconstructed using measured-attenuation correction and image reconstruction algorithms specified for each scanner. Following the scan, each image was reviewed for possible artifacts at the University of Michigan and all raw and processed study data was archived.

Subsequently, the images were normalized through a general affine model, with 12 parameters (Salas-Gonzalez et al., 2008) using the SPM5 software. After the affine normalization, the resulting image was registered using a more complex non-rigid spatial transformation model. The non-linear deformations to the Montreal Neurological Imaging (MNI) Template were parameterized by a linear combination of the lowest-frequency components of the three-dimensional cosine transform bases (Ashburner and Friston, 1999). A small-deformation approach was used, and regularization was by the bending energy of the displacement field, ensuring that the voxels in different FDG-PET images refer to the same anatomical positions in the brains. After spatial normalization, an intensity normalization was required in order to perform direct images comparisons between different subjects. The intensity of the images was normalized to a value I_{max} , obtained averaging the 0.1% of the highest voxel intensities exceeding a threshold. The threshold was fixed to the 10th bin intensity value of a 50-bins intensity histogram, for discarding most low intensity records from outside-brain regions, and preventing image saturation. The PET database collected from ADNI consists of 150 labeled PET images: 75 control subjects and 75 AD patients.

3. AR-based CAD system

Fig. 1 shows a block diagram of the proposed system that consists of two stages: (i) training stage, for AR discovery, and (ii) testing stage, for image classification of a subject under study (not

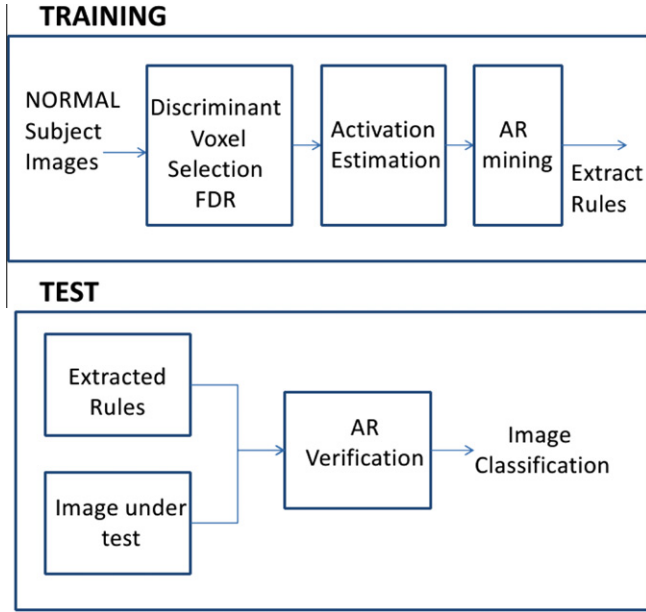


Fig. 1. Pipeline with the training and test phases of the proposed AR-based CAD system.

considered in the training stage) based on the previous extracted rules. The training process performs voxel selection, activation estimation and AR mining using a set of control subjects as follows.

3.1. Selection of discriminant regions

Each voxel of a 3-D SPECT and PET image contains information about the rCBF or glucose metabolism of the corresponding brain area, respectively. However, not all the voxels have the same level of relevance in terms of discrimination between groups of subjects. In this case, two groups of subjects are defined: Alzheimer's Disease patients, labeled as AD, and subjects not affected by this disease, labeled as NOR. Thus, an initial voxel selection based on discriminant capability is used, i.e. FDR (Álvarez et al., 2010, Ramírez et al., in press), in order to obtain a vector of discriminant voxels for each participant. In addition, the selected discriminant voxels can be used as centers of cubic blocks with an overlap between adjacent blocks for further processing.

A FDR-based masking process is performed in order to identify discriminant voxels for AR mining. This step not only improves the accuracy of the proposed method but also reduces the computational cost (Ramírez et al., in press). The FDR criterion is characterized by its separation ability as shown in Webb (2003). For the two-class case, it may be defined as follows:

$$FDR = \frac{(\mu_1 - \mu_2)^2}{\sigma_1^2 + \sigma_2^2} \quad (1)$$

where μ_i and σ_i^2 denote the i th class mean value and variance for each input variable (voxel), respectively. For a given voxel, the ratio value grows as the difference of the mean values of each two classes increases or the cumulative scattering in each class decreases, thus being useful to reveal discriminant voxels. In the case of the functional images, the voxels that satisfy a particular FDR threshold level are selected as the most discriminant variables (Álvarez et al., 2010, Ramírez et al., in press). In addition, the selection of voxels that exceeds the FDR threshold lets reduce the dimensionality of the problem, which means a lower number of input variables to the AR mining process.

Fig. 2 shows the masks for a) the average of controls as a reference, b) FDR-based SPECT mask and c) FDR-based PET mask. The latter images were obtained at a FDR threshold named h equal to 0.2, that is, just the voxels with an FDR value above 0.2 of the maximum are considered for further analysis. Note that Fig. 2a shows all the voxels, which are inside the skull, to be considered for the AR mining whereas in Fig. 2b and 2c the specific regions, depicted by the FDR criterion and used for AR discovery afterwards, are shown. This dimension reduction provides good classification results together with lower computational cost in the light of experimental results (see Section 5).

3.2. Activation estimation

After the FDR-based voxel selection process, each image is divided into 3D $v \times v \times v$ cubic blocks. The number of blocks in which an image is divided depends on two parameters: v and g . The first defines the size of the blocks, and the latter defines the size of the step, in number of voxels, between two adjacent blocks. The locations of each block define a 3D $g \times g \times g$ grid, considering the possibility of some overlap between adjacent blocks. A block is parameterized by the proportion of activated voxels t . It is considered that a block is activated if the ratio of activated voxels inside of it is greater than a given threshold.

This threshold-based activation method for block definition provides a good trade-off between computational complexity and image classification accuracy and allows the inclusion of all relevant brain regions in the detection of AD as shown in the experimental section.

3.3. AR mining

Various ensemble classification methods have been proposed in recent years for improved classification accuracy. In data mining (Agrawal and Srikant, 1994), AR-learning is an effective method for discovering interesting relationships between variables in large databases. In this context, m activated regions (ROIs) called items

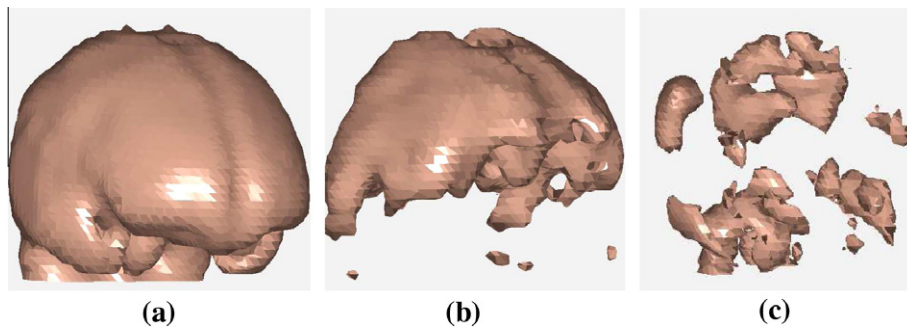


Fig. 2. 3D Mask: (a) average of controls for SPECT database, (b) FDR-mask for SPECT database, and (c) FDR-mask for PET database.

$I = \{i_1, i_2, \dots, i_m\}$ are extracted from a set of controls in an SPECT/PET database. An AR is defined as an implication or “transaction” of the form $X \Rightarrow Y$, where $X \subset I$, $Y \subset I$. It is said that the rule $X \Rightarrow Y$, which defines a relation between two activated blocks defining a *normal* pattern, has support s if $s\%$ of the transactions contain $X \cup Y$ and a confidence c , if $c\%$ of the transactions that contain X also contain Y , that is (Chaves et al., 2011):

$$\text{conf}(X \Rightarrow Y) = \frac{\text{supp}(X \cup Y)}{\text{supp}(X)} \quad (2)$$

There are different measures of significance for AR selection (Tan et al., 2002). Note that, while the support is a measure of the frequency of a rule, the confidence is a measure of the strength of the relation between sets of items (Dasseni et al., 2001).

The major goal of the proposed method is to extract and to analyze a set of discriminant ARs for an effective classification of control subjects and AD patients. AR-mining algorithms rely on support and confidence measures for discovering relationships among sets of discriminant and activated brain areas, thus enabling the design of accurate CAD systems.

4. Application to AD detection

The AR-based CAD system can be analyzed in two stages: training and testing which are described in the following and detailed in Fig. 1.

- **Training phase:** ROIs were extracted for every subject in both databases, with the FDR plus AE scheme as explained in Section 3. Afterwards, ARs are mined from a set of control subject images since the normal pattern is less variable than the AD pattern, thus they are more suitable for obtaining relevant relationships among brain regions.

The AR-mining problem is to generate all ARs that have support and confidence greater than a minimum support *minsup* and minimum confidence *minconf* value established by the user. If the values of *minsup* and *minconf* increase, the number of mined rules is reduced. Moreover, if *minconf* and *minsup* are set close to the maximum 100% (as shown in the experimental Section 5) the set of mined rules contains the most discriminant relationships.

In addition, ARs are mined by means of leave-one-out (loo) cross-validation strategy (Gidskehaug et al., 2008), that is, if a given control subject is being evaluated, it is not taken into account in the AR mining process.

- **Testing phase:** after the AR mining process, the number of rules verified by each subject is checked as shown in Fig. 1. Since ARs are mined from controls, it is expected that control subjects verify more rules than AD patients. The system computes the number of rules verified by a subject under study. In this way, a subject is classified as normal if the number of verified rules is above a fixed threshold ($\# \text{ verified rules} > \text{threshold}$), otherwise it is classified as AD.

Finally, the accuracy (Acc), sensitivity (Sen) and specificity (Spe) are estimated by means of loo cross-validation. Note that, sensitivity of a classifier measures the proportion of true-positive correctly detected, while specificity is defined as the proportion of true negatives detected as such.

5. Evaluation experiments and discussion

Several experiments were conducted in order to test the reliability of the proposed AR-based classifier. Two image modality databases (SPECT and PET) were used in the analysis in order to highlight its generalization ability. ROIs were selected as $5 \times 5 \times 5$ -voxel 3D blocks located inside the corresponding SPECT or PET FDR mask. An FDR threshold $h = 0.2$ was selected. The center coordinates of the 3D blocks are restricted to be in $2 \times 2 \times 2$ 3D grid.

At the feature extraction stage, a 3D block is defined as activated if more than a fraction (50 voxels) of the total (125 voxels) are activated. This threshold represents a 40% of activated voxels and allows only brain volumes with a high activation to be considered as ROIs. For both databases, the activation threshold is reduced when the FDR mask is used since it locates itself the most discriminant voxels for the early detection of the AD.

Fig. 3 shows coronal, transaxial and sagittal slices of a mean control PET image illustrating the voxels within the FDR mask (crosses) as well as the activated ROIs representing the ARs (squares), which are enlarged in the lower part of the Fig. 3 for clarity. Note that, these ROIs correspond to those regions commonly

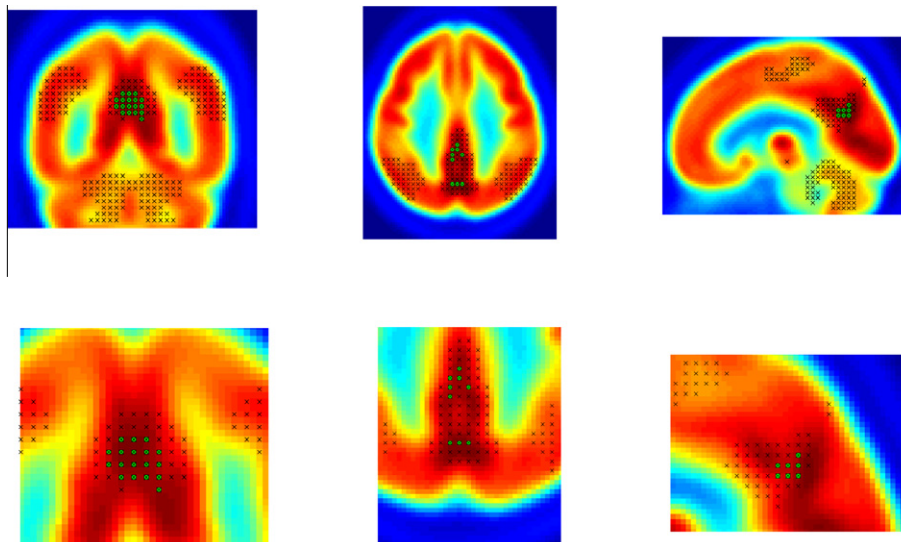


Fig. 3. Bidimensional activated regions from coronal, axial and sagittal slices.

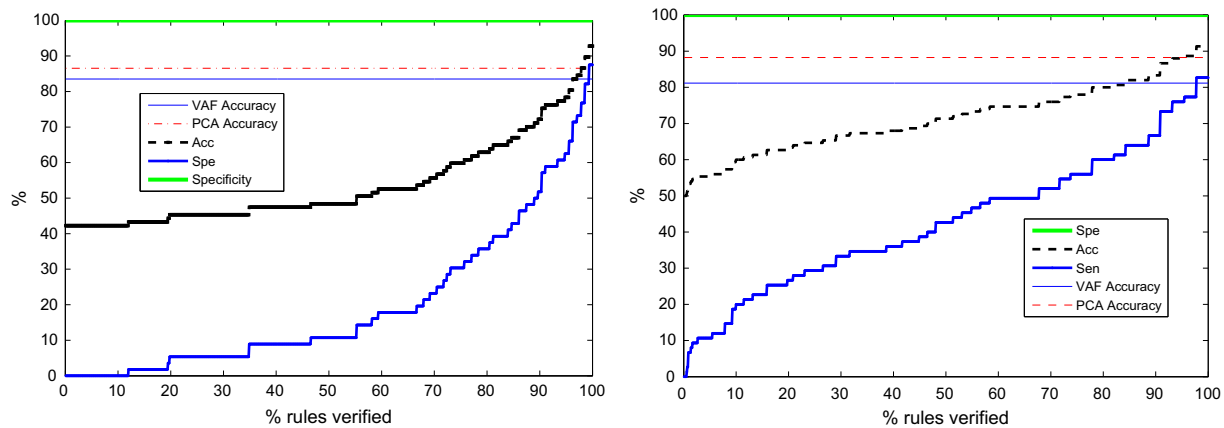


Fig. 4. Accuracy, sensitivity and specificity values as a function of the threshold of verified rules in (%) for (a) SPECT (b) PET. Comparison to other recently reported methods.

affected by AD, i.e. the posterior cingulate gyri and precunei, as well as the temporo-parietal region (López et al., 2011).

ARs are mined from controls using the highest *minsup* and *minconf*, that is 100%, in order to extract the “most common pattern” in normal subjects and to provide an improved detection ability in the early diagnosis of AD. The experiments considered an increasing threshold for the number of verified rules by each subject as shown in Fig. 4. It shows the accuracy, sensitivity and specificity of the proposed CAD system as a function of the classification threshold (number of rules verified by each subject). In addition, a comparison to other recently reported methods including voxel-as-features (VAF) (Fung and Stoeckel, 2007) or principal component analysis (PCA) in combination with a support vector machine (SVM) classifier (Álvarez et al., 2009) is shown.

The accuracy, specificity and sensitivity values converge to a maximum of 92.78%, 100% and 87.5% for SPECT and 91.33%, 100% and 82.67% for PET, respectively. The classification accuracy improves when increasing the threshold of verified rules by each subject since a higher number of rules are required to be fulfilled to classify any subject under test as normal, thus more AD patients are correctly detected. In particular, 67860 rules represent the maximum number of verified rules (denoted by 100% in the x-axis in Fig. 4) for SPECT, while for PET, this number reaches 7482 rules (see Table 1). As a conclusion, the size of the area under study derived from the FDR analysis in SPECT is wider than in PET where functional deficits are more localized in well known brain regions. Thus, the number of ROIs used as inputs for the AR mining process is higher for SPECT because of the size of the activation map mask.

It is also observed that the specificity values for this CAD system reach 100%, that is, all controls are correctly classified when the *minsup* and *minconf* values in the AR mining process are equal to 100%. These results are in agreement with the expected behaviour of the system since normal subjects are assumed to have a common image pattern and to verify most of the mined ARs. Finally, it can be concluded that the proposed system outperforms recent developed CAD systems based on VAF and PCA (Álvarez et al.,

2009., 2010) that yield lower image classification accuracies of 83% or 86% for SPECT and 81.18% or 88.24% for PET, respectively.

The receiver operating characteristic (ROC) curves have shown to be very effective for the evaluation of CAD systems. These plots show the trade-off between the specificity and sensitivity of the CAD system as the detection threshold varies. Fig. 5 shows the ROC curves of the proposed FDR AR-based CAD system as well as baseline VAF and PCA methods for the SPECT and PET databases.

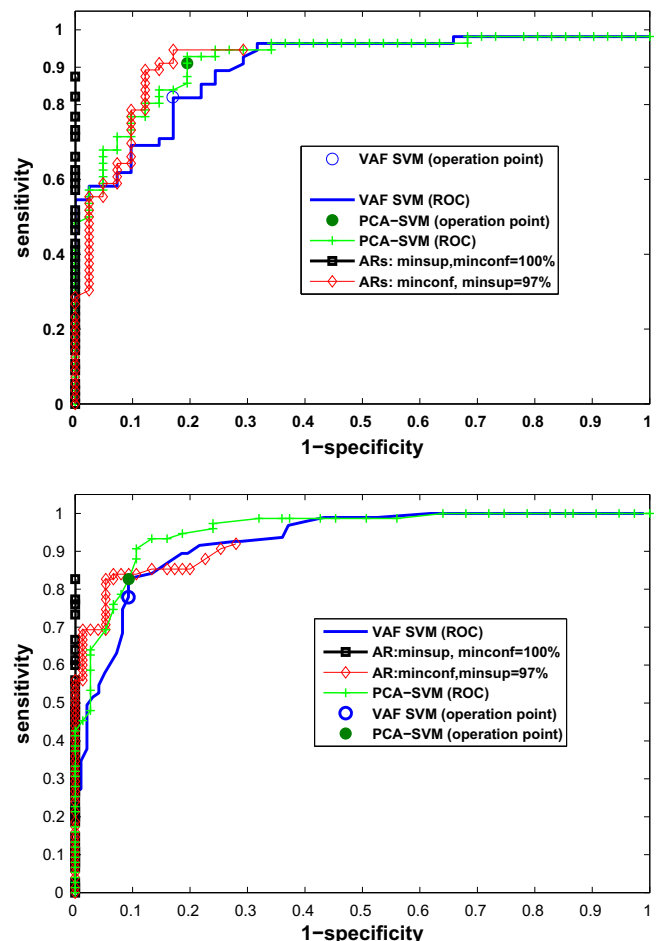


Fig. 5. ROC Curve for (a) SPECT and (b) PET databases. Comparison to other recently reported methods.

Table 1
Comparison of maximum Accuracy and number of mined ARs obtained for SPECT and PET databases for different thresholds of the FDR voxel selection mask.

	$h = 0.2$	$h = 0.4$	$h = 0.6$	$h = 0.8$
PET: Max number of mined rules	7482	5256	1332	210
PET: Acc (%)	91.33	90.67	88.67	84.00
SPECT: Max number of mined rules	67860	132	0	0
SPECT: Acc (%)	92.68	65.98	–	–

The proposed method at 100% *minconf* and *minsup* outperforms several recently reported CAD systems, i.e. VAF or PCA (López et al., 2009, Álvarez et al., 2010), since its ROC is shifted up to the left in the ROC space. In fact, the proposed method yields 87.5% and 82.67% sensitivity for SPECT and PET modalities, respectively, and 100% specificity. Fig. 5 also shows the ROC curve of the proposed method for 97% *minconf* and *minsup*. In this case, the AR-based method reports lower accuracy rate than the previous model configuration, however this analysis provides useful information for parameter selection.

One of the advantages of the proposed AR-based CAD system is the reduced complexity of the decision rule that consists of an AR checking process of the SPECT or PET image under study. Moreover, constraining ARs to be defined over brain volumes inside an FDR mask reduces the complexity of the problem. In this case, only relevant brain areas are subjected to AR discovery saving the evaluation of the Apriori algorithm on irrelevant activated regions, i.e. cerebellum.

Finally, the trade-off between computational cost and detection ability was studied in order to analyze the computational demands of the proposed method. Table 1 shows the computational cost of the proposed system in terms of the number of ARs mined for a given FDR threshold h . Note that, this threshold is used as a voxel selection criterion and enables reducing the dimension of the input variables in the AR mining process. The accuracy of the system improves by reducing the threshold h at the cost of increasing the number of mined ARs and, subsequently, the computational complexity. The best trade-off between classification results and complexity is obtained for a threshold $h = 0.2$.

6. Conclusion

ARs were investigated for classification of functional images and the design of CAD systems. An FDR mask not only enabled selecting the most discriminant regions for further analysis and improving the classification results, but also reduced the computational cost. ARs were mined from normal patterns and the decision rule of the CAD system was formulated in terms of the number of “common” rules verified by each subject.

Several experiments were conducted in order to test the reliability of the proposed AR-based classifier. Two medical image modality databases (SPECT and PET) were used in the analysis in order to highlight the generalization ability of the CAD system. The proposed method outperformed recently reported methods (i.e. VAF or PCA) in terms of accuracy, sensitivity and specificity and converged to a optimum operating point when the number of verified ARs was sufficiently high (including all the rules associated with reported brain regions that are relevant in early AD detection). In this way, it yielded an accuracy, specificity and sensitivity up to 92.78%, 100% and 87.5%, respectively, for SPECT, and 91.33%, 100% and 82.67%, for PET, when 100% minimum support and confidence were selected. Moreover, this CAD system was defined as an offline method, since the rules were obtained by means of the Apriori algorithm from a set of control subjects and every test subject was evaluated by means of the same set of rules.

Acknowledgments

This work was partly supported by the MICINN under TEC2008–02113 and the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain) under the Excellence Project (P07-TIC-2566, P09-TIC-4530 and P11-TIC-7103). We are grateful to M. Gómez-Río and coworkers from the “Virgen de las Nieves” hospital in Granada (Spain) for providing and labeling the SPECT images used in this work. The PET Data collection and sharing for this project

was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, Glaxo-SmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffmann–La Roche, Schering-Plough, Synarc, Inc., as well as non-profit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (<http://www.fnih.org>). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH Grants P30 AG010129, K01 AG030514, and the Dana Foundation. The authors are grateful to the reviewers for their helpful advices and valuable suggestions to improve the quality of the work provided in this document.

References

- Agrawal, R., Srikant, R., 1994. Fast Algorithms for mining Association rules. In: Int. Conf. VLDB, Santiago de Chile, Chile, pp. 487–499.
- Álvarez, I., Górriz, J.M., Ramírez, J., Salas-Gonzalez, D., López, M., Puntonet, C.G., Segovia, F., 2009. Alzheimer's diagnosis using eigenbrains and support vector machines. *Electron. Lett.* 45 (7), 342–343.
- Álvarez, I., Górriz, J.M., Ramírez, J., Salas-Gonzalez, D., López, M., Segovia, F., Chaves, R., Gómez-Río, M., Puntonet, C.G., 2010. 18 F-FDG PET imaging analysis for computer aided Alzheimer's diagnosis. *Inform. Sci.* 181 (4), 903–916.
- Álvarez, I., M.Górriz, J., López, M.M., Ramírez, J., Salas-Gonzalez, D., Segovia, F., Chaves, R., Puntonet, C.G., 2011. Computer aided diagnosis of Alzheimer's Disease using component based SVM. *Appl. Soft Comput.* 11 (2), 2376–2382.
- Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. *Hum. Brain Mapp.* 7 (4), 254–266.
- Braak, H., Braak, E., 1997. Diagnostic criteria for neuropathologic assessment of Alzheimer's Disease. *Neurobiology Aging* 18 (4), S85–S88.
- Chaves, R., Ramírez, J., Górriz, J.M., López, M., Salas-Gonzalez, D., Álvarez, I., Segovia, F., 2009. SVM-based computer-aided diagnosis of the Alzheimer's Disease using t -test NMSE feature selection with feature correlation weighting. *Neuroscience Lett.* 461 (3), 293–297.
- Chaves, R., Górriz, J.M., Ramírez, J., Illán, I.A., Salas-González, D., Gómez-Río, M., 2011. Efficient mining of association rules for the early diagnosis of Alzheimer's Disease. *Phys. Med. Biol.* 56 (18), 6047–6063.
- Dasseni, E., Verykios, V.S., Elmagarmid, A.K., Bertino, E., 2001. Hiding association rules by using confidence and support. *Lect. Notes Comput. Sci.* 2137, 369–383.
- Friston, K.J., Ashburner, J., Kiebel, S.J., Nichols, T.E., Penny, W.D., 2007. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Academic Press.
- Fung, G., Stoessel, J., 2007. SVM feature selection for classification of SPECT images of Alzheimer's Disease using spatial information. *Knowl. Inform. Syst.* 11 (2), 243–258.
- Gidskehaug, L., Anderssen, E., Alsberg, B.K., 2008. Cross model validation and optimisation of bilinear regression models. *Chemometr. Intell. Lab. Syst.* (93), 1–10.
- Karabatak, M., Cevdet Ince, M., 2009. A new feature selection method based on association rules for diagnosis of erythemato-squamous diseases. *Expert Syst. Appl.* 36 (10), 12500–12505.
- López, M., Ramírez, J., Górriz, J.M., Salas-Gonzalez, D., Álvarez, I., Segovia, F., Puntonet, C.G., 2009. Automatic tool for the Alzheimer's Disease diagnosis using PCA and bayesian classification rules. *IET Electron. Lett.* 45 (8), 389–391.
- López, M., Ramírez, J., Górriz, J.M., Álvarez, I., Salas-Gonzalez, D., Segovia, F., Chaves, R., Padilla, P., Gómez-Río, M. for the Alzheimer's Disease Neuroimaging Initiative, 2011. Principal component analysis-based techniques and supervised classification schemes for the early detection of Alzheimer's Disease. *Neurocomputing* 74 (8), 1260–1271.
- Nestor, P.J., Scheltens, P., Hodges, J.R., 2004. Advances in the early detection of Alzheimer's Disease. *Nat. Rev. Neurosci.* 4, S34–S35.
- Ramírez, J., Górriz, J.M., Chaves, R., Salas-Gonzalez, D., López, M., Salas-Gonzalez, D., Álvarez, I., Segovia, F., 2009. SPECT image classification using random forests. *IET Electron. Lett.* 45 (12), 604–605.
- Ramírez, J., Górriz, J.M., Salas-Gonzalez, D., Romero, A., López, M., Illán, I.A., Gómez-Río, M., in press. Computer-aided diagnosis of Alzheimer's type dementia combining support vector machines and discriminant set of features. *Inform. Sci.*, <http://dx.doi.org/10.1016/j.ins.2009.05.012>.

- Ribeiro, M.X., Bugatti, P.H., Traina Jr., C., Marques, P., Rosa, N.A., Traina, A., 2009. Supporting content-based image retrieval and computer-aided diagnosis systems with association rule-based techniques. *Data Knowl. Eng.* 68 (12), 1370–1382.
- Salas-Gonzalez, D., Górriz, J.M., Ramírez, J., Lassl, A., Puntonet, C.G., 2008. Improved gauss-newton optimization methods in affine registration of SPECT brain images. *IET Electron. Lett.* 44 (22), 1291–1292.
- Tan, P., Kumar, V., Srivastava, J., 2002. Selecting the right interestingness measure for association patterns. *8th ACM SIGKDD Conf. Knowl. Discovery Data Mining* pp. 32–41.
- Turkeltaub, P., Eden, G., Jones, K., Zeffiro, T., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* 16 (3), 765–780.
- Webb, A.R., 2003. *Statistical Pattern Recognition*, Second ed. Wiley.