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

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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.

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 [^{18}F] Fluorodeoxyglucose. In AD, characteristic brain regions show decreased glucose metabolism, specifically bilaterally regions in the temporal and parietal lobes, posterior cingulate gyri and precunei, 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

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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