Independent Component Analysis-Based Classification of Alzheimer’s Disease MRI Data

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Abstract. There is an unmet medical need to identify neuroimaging biomarkers that allow us to accurately diagnose and monitor Alzheimer’s disease (AD) at its very early stages and to assess the response to AD-modifying therapies. To a certain extent, volumetric and functional magnetic resonance imaging (fMRI) studies can detect changes in structure, cerebral blood flow, and blood oxygenation that distinguish AD and mild cognitive impairment (MCI) subjects from healthy control (HC) subjects. However, it has been challenging to use fully automated MRI analytic methods to identify potential AD neuroimaging biomarkers. We have thus proposed a method based on independent component analysis (ICA) for studying potential AD-related MR image features that can be coupled with the use of support vector machine (SVM) for classifying scans into categories of AD, MCI, and HC subjects. The MRI data were selected from the Open Access Series of Imaging Studies (OASIS) and the Alzheimer’s Disease Neuroimaging Initiative databases. The experimental results showed that the ICA method coupled with SVM classifier can differentiate AD and MCI patients from HC subjects, although further methodological improvement in the analytic method and inclusion of additional variables may be required for optimal classification.

Keywords: Alzheimer’s disease, independent component analysis, magnetic resonance imaging, mild cognitive impairment, neuroimaging biomarker, support vector machine

INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia associated with aging. Postmortem studies of AD have showed three typical lesions in AD brains: intraneuronal neurofibrillary tangles (NFTs),...
extracellular deposits of amyloid-β (Aβ) plaques, and the loss of neurons [1, 2]. To clinically diagnose AD patients at an early stage, many biomedical imaging techniques have been used, including structural magnetic resonance imaging (sMRI) [3], functional magnetic resonance imaging (fMRI) [4], and positron emission tomography (PET) [5].

Structural MRI promises to aid in the diagnosis and treatment monitoring of mild cognitive impairment (MCI) and AD through the facile detection of surrogate biomarkers for disease state classification. Studies involving the analyzing of sMRI brain scans can be generally categorized into two classes: region-of-interest (ROI) analysis [6] and whole brain analysis [7, 8]. ROI analysis focuses on specific brain regions, especially the hippocampus and the entorhinal cortex [9, 10], to show histopathological changes at early stages of AD [11]. ROI analysis of the brain structure is considered a gold standard, but it has some drawbacks such as operator-dependency, labor- and time-intensiveness, and the required step of a priori choice of regions for investigation [12]. To overcome these shortcomings, some automated methods of measuring whole brain atrophy have been developed, such as voxel-based morphometry (VBM) [8], tensor-based morphometry [13], and source-based morphometry [14]. However, sMRI researchers are often divided in choosing methods from the following image analysis approaches: volume statistics [6, 9], cortex shape analysis [10], and blind signal separation/machine learning techniques [5, 7, 15, 16].

Independent component analysis (ICA), an important blind signal separation technique, has proved to be a powerful method for analyzing neuroimage data [16, 17]. It is one of the multivariate and data-driven techniques that enable an exploratory analysis of MRI datasets to extract useful information about the relationships among voxels in local brain substructures. For the diagnosis or classification of AD and MCI patients, support vector machine (SVM), one of the machine learning techniques, has also received much attention [7, 15].

In the current study, we have applied the ICA-based method coupled with the SVM technique to selected MRI data from both the OASIS and ADNI databases. The ICA-based method has three steps. First, all MRI scans are aligned and normalized by statistical parametric mapping (SPM). Then, ICA is applied to the images for extracting specific neuroimaging components as potential classifying features. Finally, the separated independent component coefficients are fed into the SVM classifying machine that discriminates among AD, MCI, and healthy control (HC) subjects. Our results indicate that the proposed method is able to classify AD and MCI patients and HC subjects with certain accuracy. To our knowledge, the application of the ICA-based feature extraction method coupled with the SVM-based data classifier for anatomical MRI data analysis of the AD brain has not been reported before.

MATERIALS AND METHODS

MRI databases

In the study, we will use MRI data from two image datasets: the OASIS and the ADNI.

The Open Access Series of Imaging Studies (http://www.oasis-brains.org/) is made available by the Washington University Alzheimer’s Disease Research Center; Dr. Randy Buckner at the Howard Hughes Medical Institute (HHMI) at Harvard University; the Neuroinformatics Research Group (NRG) at Washington University School of Medicine; and the Biomedical Informatics Research Network (BIRN). Their aim is to make brain MRI datasets freely available to the scientific community. The dataset consists of a cross-sectional collection of 416 subjects aged between 18 and 96 years old, including 218 subjects aged between 18 and 59 years old, and 198 subjects aged between 60 and 96 years old. Of the older subjects, 98 had a Clinical Dementia Rating (CDR) score of 0, indicating no dementia; and 100 had a CDR score greater than zero (70 CDR = 0.5, 28 CDR = 1, 2 CDR = 2), indicating a diagnosis of very mild to moderate AD.

In our analysis, the whole data set in the OASIS database is divided into four groups: AD (100 subjects with the CDR score greater than 0), young healthy controls (yHC, 116 subjects), middle age healthy controls (mHC, 100 subjects), and old healthy controls (oHC, 100 subjects), respectively. The age range, mean and standard deviation (sd) for different control groups are: yHC, range = 18–24 and mean ± sd = 21.33 ± 3.33; mHC, range = 25–59 and mean ± sd = 42.16 ± 17.16; and oHC, range = 60–94 and mean ± sd = 75.58 ± 18.42. The more detailed statistics of the dataset were described in the literature [18].

Launched in 2003, the ADNI’s [http://www.loni.ucla.edu/ADNI/] [3] primary goal has been to test whether serial MRI, PET, fluid biological markers in cerebrospinal fluid (CSF) and blood, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Subjects have been recruited from approximately 50 sites across the United States and Canada. The ADNI has
recruited over 800 adults, aged between 55 and 90 years old, to participate in the research. These include approximately 200 cognitively normal individuals who are followed for 3 years, 400 subjects with MCI who are followed for 3 years, and 200 patients with early AD who are followed for 2 years. In our analysis, MRI data of 202 AD, 410 MCI, and 236 HC subjects were used.

The framework of the proposed method

The framework of our proposed brain MRI data analysis method is shown in Fig. 1. This includes MRI data preprocessing, normalization and segmentation, ICA-based image decomposition and feature extraction, and SVM-based classification steps.

MRI data preprocessing, image normalization, and segmentation

For all MRI images from the OASIS and ADNI databases, we pre-processed them and then normalized the MRI images of each subject into a standard space defined by the template image T1.nii supplied with the SPM8 toolbox. The detailed configurations included: source image smoothing with 8 mm, affine regularization with the ICBM (International Consortium for Brain Mapping) space template, a nonlinear frequency cutoff of 25, 16 nonlinear iterations, and trilinear interpolation. Finally, we extracted the sub-volumes within the bounding box of (–79–80, –112 79, –74–85 in mm) relative to the anterior commissure in the space described in the atlas of Talairach and Tournoux [19]. Therefore, all MRI images were normalized into $160 \times 192 \times 160$ voxel-wise images.

To further analyze the MRI images, the gray matter of the brain was first analyzed to check the degree of significance in discriminating AD and MCI from HC. First, the whole brain MRI image was segmented by segment module in SPM8 into three parts: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The images were then subjected to the ICA and SVM steps as described in the following sections.

Fig. 1. The methodological framework for the analysis of structural MRI data. First, all MR images are normalized into a template as aforementioned in the MRI data preprocessing section. Next, the normalized brain images are decomposed into MRI basis functions and the corresponding coefficients using the FastICA algorithm [21, 22]. Finally, the resulting coefficients are fed into a SVM-based classifier for the diagnosis of individuals as AD, MCI, or HC subjects.
The spatial ICA model for MRI images is shown in Fig. 2. In the study, the MRI images have been processed by the FastICA algorithm [21, 22], as described in Table 1. The decomposed independent coefficients were viewed as the representations in the ICA subspace. After ICA computation, any MRI image can be reconstructed by linearly combining the set of basis functions and the corresponding coefficients, for example, as shown in Fig. 3.

**Classification using support vector machine (SVM)**

Support Vector Machine [23], a very popular classifier, is a supervised learning method used for data classification and pattern recognition and has been recently used to distinguish AD subjects from elderly HC subjects using anatomical MRI images [7].
SVM conceptually implements the idea that vectors are linearly or nonlinearly mapped to a very high dimension feature space. In this feature space, a linear separation surface is created to separate the training data by minimizing the margin between the vectors of the two classes. We used the LIBSVM (http://www.csie.ntu.edu.tw/~cjlin/libsvm) as the classifier to differentiate AD or MCI patients from HC subjects.

Taking the influence of the number of training samples on classification accuracy into account, all the datasets are divided into two groups: training and testing dataset. Two ratios of training sets are compared: 75% training set versus 25% testing set, and 90% training set versus 10% testing set. The mean classification accuracy was obtained after we repeated the experiments over 100 times by randomly selecting training and testing datasets.

Finally, the same experimental methods were applied to the whole brain MRI images also (without segmentation).

RESULTS

We have performed several analyses using the MRI images from the OASIS and ADNI databases to verify the performances of the proposed method, such as feature extraction, representation, and discrimination of AD and MCI subjects from HC subjects. To further validate the proposed method, we have applied the method to analyze gray matter of the MRI images in the OASIS and ADNI databases.

Experiment 1: Feature extraction and representation

Using the FastICA algorithm to decompose brain MR images, we can obtain MRI image basis functions and corresponding coefficients. From these bases shown in Fig. 4, it should easily be noticed that each base has only coded a local part of the brain MRI.

Fig. 4. Learned MR image bases achieved by FastICA algorithm. This figure shows the examples of learned MR image bases from MRI data with AD and HC subjects using a spatial ICA algorithm built into the FastICA toolbox.
images. Different bases locally code different parts of the brain images. If a corresponding coefficient is significant, we can draw a conclusion that the base is more important in the individual MRI scans.

For the convenience of viewing the manifold distribution of MRI images, we project all MRI scan samples onto the ICA feature subspace. The dimensionality of the separated coefficients is reduced using principal component analysis (PCA) [24]. Only the first three maximum principal components are shown in three-dimensional space in Fig. 5.

Figure 5A shows the distribution of MRI data on the 3D subspace spanned by age, principal component 1 (PC1), and principal component 2 (PC2). Here, PC1 and PC2 are reconstructed from decomposed components using PCA. And Fig. 5B denotes distribution in a 3D subspace of PC1, PC2, and PC3, with the same meaning as Fig. 5A. The two figures indicate that the brains are different and gradually change with age. The results are consistent with that presented by Marcus et al. [18].

**Experiment 2: Classification of OASIS MRI data**

The independent coefficients separated by FastICA can be considered as the representation of MRI images in the subspace of ICA and are used by the SVM classifier to discriminate AD from yHC, mHC, and oHC. We have conducted two experiments on the dataset. One uses the whole brain MRI images, and the other uses the GM images extracted from the whole brain images.

The mean classification accuracy, sensitivity, specificity, and their corresponding standard deviations are shown in Tables 2 and 3, respectively. In Table 2, the experimental data are for the whole brain images. In Table 3, the experimental data are for gray matter extracted from the whole brain images, and other experiment parameters are the same as that of the whole brain images. From these tables, it is noted that the differences between AD and other control groups are greater as the age gap increases as expected.

**Experiment 3: Classification of ADNI MRI data**

Using the aforementioned experimental methods, all images (202 AD, 410 MCI, and 236 HC) in the ADNI dataset were analyzed. The classification accuracy, sensitivity, and specificity of these images are shown in Table 4.
Table 4
Classification accuracy of whole brain images from the ADNI (%)

<table>
<thead>
<tr>
<th>Training sets</th>
<th>Parameters</th>
<th>AD vs. HC (mean ± sd)</th>
<th>MCI vs. HC (mean ± sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% Accuracy</td>
<td>75.0 ± 2.4</td>
<td>67.2 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>71.1 ± 4.9</td>
<td>68.2 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>78.3 ± 5.4</td>
<td>66.3 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>90% Accuracy</td>
<td>76.9 ± 5.2</td>
<td>72.0 ± 3.5</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74.0 ± 8.5</td>
<td>71.3 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>79.5 ± 6.3</td>
<td>72.7 ± 7.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 5
Classification accuracy of gray matter images from the ADNI (%)

<table>
<thead>
<tr>
<th>Training sets</th>
<th>Parameters</th>
<th>AD vs. HC (mean ± sd)</th>
<th>MCI vs. HC (mean ± sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% Accuracy</td>
<td>75.3 ± 2.6</td>
<td>70.8 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75.4 ± 6.9</td>
<td>72.8 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>75.2 ± 6.5</td>
<td>66.1 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>90% Accuracy</td>
<td>80.7 ± 3.0</td>
<td>71.1 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81.9 ± 7.2</td>
<td>73.2 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>79.5 ± 7.3</td>
<td>68.6 ± 7.2</td>
<td></td>
</tr>
</tbody>
</table>

database can be classified into two categories: AD vs. HC and MCI vs. HC. The resulting mean classification accuracy, sensitivity, specificity, and their corresponding standard deviations are shown in Tables 4 and 5, respectively.

Analysis of the results

From the result tables, three points must be assessed. First, in Tables 2 and 3, the mean classification accuracy is descended by the age from AD versus yHC, mHC, and oHC. It can be explained that our proposed method can detect the MR image feature changes of diseased brains caused by AD or other neurological diseases. During the preprocessing steps of alignment and spatial normalization, some individual information is missing, such as the size of the hippocampus and other brain tissues. The minor changes of the local area in the brain are probably submerged under the greater stability of the whole brain tissues in the statistical ICA method. Second, the results from the 75% and 90% training sets support the idea that the larger the training set is, the higher its mean classification accuracy. Third, comparing the results of the whole brain with GM, the classification results from GM is not more significant than the classification results from the whole brain images between AD and NC subjects.

DISCUSSION

Herein we have demonstrated that the fully automatic method based on ICA coupled with SVM for MRI data analysis is very useful in discriminating among AD, MCI, and HC subjects. This study is comparable with other relevant works. Due to the inherent differences of the OASIS and ADNI datasets, we thus have not the same study objectives when using the data. In analyzing OASIS data, we have focused upon classification of AD vs. HC subjects with a range of different age groups-yHC, mHC, and oHC. While analyzing ADNI data, we intend to classify AD and MCI versus age-matched HC subjects.

Why applying ICA to structural image analysis is important?

ICA is one of the data-driven, multivariate, and unsupervised methods with an advantage of using no a priori information. It has become an increasing popular biomedical data-mining technique as well as a processing method for functional and structural MRI data. To our knowledge, there is no report on the application of ICA to structural MRI data from AD patients. However, ICA might also be a useful tool for early AD diagnosis of sMRI data analysis because it has shown its usefulness in processing sMRI data from schizophrenia patients [16]. Therefore, in this study, we have applied ICA to the analysis of AD-related sMRI data. Experimental results on MRI data from the OASIS and ADNI databases have indicated that the proposed method based on ICA coupled with SVM is a useful tool for classifying AD, MCI, and HC subjects.

Comparison with other related work

Marcus and colleagues [18] used the FAST program in the FSL software suite (http://www.fmrib.ox.ac.uk/fsl) to compute normalized whole-brain volume (nWBV) and a plotted nWBV distribution line across the adult life span in the OASIS database. Our results shown in Fig. 5 are similar to that presented in their paper, indicating that the feature extraction method based on ICA preserves the useful changing information with the development of AD. Therefore, there are the same manifolds in both the original statistical space (nWBV-ages) and the ICA subspace.

Garcia-Sebastian et al. [25] studied the feature extraction processes based on VBM analysis to classify the MRI volumes of AD patients and HC subjects. They applied SVM to perform classification on the MRI volumes of 98 females and obtained better results with 80.6–87.5% accuracy. Savio and collaborations [26] applied four different models of Artificial Neural Networks (ANNs) to the same dataset and reported the result of 83% classification
Our main goal in the current study is to verify the performances of the proposed method based on ICA coupled with SVM. Much work lies ahead, however. We have presented the basis functions, or features, but questions such as: What is the exact meaning of these features? Which feature is more important, or how are the features important in terms of any interrelation-ship? How many features are related to AD? What are the effects of the age, gender, and amyloid pathology on the features?, have not yet been addressed. Therefore, our future work will focus on answering these questions. In addition, the classification results we have achieved can only be considered as “putative surrogate image biomarkers” as they are subjected to further validation due to the exploratory nature of our proposed methods. In the future studies, we will aim for achieving ≥85% mean accuracy, specificity, and sensitivity in MRI data classification of AD and MCI versus age-matched HC subjects, depending upon further methodology refinements. Further, we would like to perform a result comparison with results from other published semi-automated methods. Moreover, the ADNI has provided follow-up MRI data; therefore, we would like to apply the proposed method to the longitudinal analysis of all of these MRI data next.

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Partial data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). 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 available at: http://adni.loni.ucla.edu/research/active-investigators/.


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