Neuroscience Letters 550 (2013) 17–22

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Dimensionality reduced cortical features and their use in predicting longitudinal changes in Alzheimer's disease

Hyunjin Park[a], Jin-ju Yang[b], Jongbum Seo[c], Jong-min Lee[b,*], the ADNI[1]

[a] School of Electronic Electrical Engineering, Sungkyunkwan University, Republic of Korea
[b] Department of Biomedical Engineering, Hanyang University, Seoul, Republic of Korea
[c] Department of Biomedical Engineering, Yonsei University, Republic of Korea

HIGHLIGHTS

- Cortical features provide information to distinguish Alzheimer's from normal.
- Cortical thickness and sulcal depth were used.
- Manifold learning using PCA reduced the dimensionality of the cortical feature.
- The dimensionality reduced features were used to predict conversion to AD.
- SVM classifiers were used with the reduced cortical features.

ARTICLE INFO

Article history:
Received 9 November 2012
Received in revised form 9 April 2013
Accepted 20 June 2013

Keywords:
Cortical feature
Cortical thickness
Sulcal depth
Manifold learning
Early prediction
Alzheimer's disease

ABSTRACT

Neuroimaging features derived from the cortical surface provide important information in detecting changes related to the progression of Alzheimer's disease (AD). Recent widespread adoption of neuroimaging has allowed researchers to study longitudinal data in AD. We adopted cortical thickness and sulcal depth, parameterized by three-dimensional meshes, from magnetic resonance imaging as the surface features. The cortical feature is high-dimensional, and it is difficult to use directly with a classifier because of the "small sample size" problem. We applied manifold learning to reduce the dimensionality of the feature and then tested the usage of the dimensionality reduced feature with a support vector machine classifier. Principal component analysis (PCA) was chosen as the method of manifold learning. PCA was applied to a region of interest within the cortical surface. We used 30 normal, 30 mild cognitive impairment (MCI) and 12 conversion cases taken from the ADNI database. The classifier was trained using the cortical features extracted from normal and MCI patients. The classifier was tested for the 12 conversion patients only using the imaging data before the actual conversion. The conversion was predicted early with an accuracy of 83%.

1. Introduction

Recent advances in neuroimaging techniques such as high-resolution magnetic resonance imaging (MRI) have revealed detailed information about the cortex. Study of shape, known as morphometry, has been successfully applied to distinguish AD from normal controls [11]. Recent widespread adoption of neuroimaging has allowed researchers to study longitudinal data in AD. Researchers can assess shape information from different time points to compute the temporal changes in shape information for a given patient in longitudinal data. Many researchers have adopted a method known as voxel based morphometry (VBM) [1]. VBM is typically applied to 3D volume data. Surface features derived from brain cortex have also been adopted to distinguish demented patients from normal controls. Cortical thickness, sulcal depth, surface area, and mean curvature computed from the cortical surface have been applied to distinguish AD from normal controls [10,19]. The cortex is a complexly folded two 2D sheet embedded in a 3D space, typically modeled using a set of 3D polygonal meshes. Tens of thousands of vertices are used to form a cortical surface in many implementations. All the features defined on the cortical surface can be pooled and treated as one high-dimensional feature vector, which is commonly done in machine learning. *N* feature vectors, whose dimensionality is in the tens of thousands, would be generated to study *N* patients. Neuroimaging studies tend to have less than few hundred patients in a study. Thus, the number of

* Corresponding author. Tel.: +82 2 2220 0697; fax: +82 2 2296 5943.
E-mail addresses: ljm@hanyang.ac.kr, jmlee@bme.hanyang.ac.kr (J.-m. Lee).

[1] Data used this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.06.042

observations is far less than the dimensionality of the features, which would lead to unreliable classifier performance [6,7,15]. This problem of unsatisfactory classifier performance is known as the "small sample size" problem. The dimensionality of the feature vector may be reduced by using manifold learning methods. As a result, handling of shape information becomes more tractable in a low dimensional space. PCA was applied to the high dimensional cortical features in this study. We chose cortical thickness and sulcal depth as our features since these two features have been effective for reflecting shape changes related to AD and MCI [10]. PCA was applied to the features defined on the whole cortex and the features defined on a specific ROI. ROI was automatically defined by choosing a set of vertices with high discriminative power to distinguish demented scans from normal controls. The features whose dimensions were reduced were fed into a support vector machine (SVM) classifier. SVM is one of the state-of-the-art classifiers currently available with a proven track record [2]. Many excellent papers applied PCA or methods similar to PCA for feature extraction and then used the extracted features with a modern classifier to distinguish AD from normal controls [4,8,14,15,17]. López et al. adopted kernel PCA and linear discriminant analysis (LDA) for feature extraction of SPECT voxel values and used the extracted features with the SVM classifier [14]. Ramírez et al. adopted partial least square (PLS) regression for feature extraction of SPECT voxel values and used random forest method for prediction [17]. Graña et al. applied Pearson's correlation to diffusion tensor imaging and selected voxels with high discriminative power [8]. Then the selected voxels were used as input to the SVM classifier. They adopted fractional anisotropy and mean diffusivity as features derived from the diffusion tensor imaging. Chaves et al. applied voxel-wise *T*-tests to find voxels with good normalized mean squared error features and used the selected voxels as input to the SVM classifier in SPECT [4]. López et al. applied PCA and LDA for feature extraction of SPECT or PET voxel values and used the extracted features with SVM or neural network classifier [15]. The SPECT and PET scans were obtained from the ADNI database. The main difference between our approach and the existing work is that we used cortical features while the others adopted volumetric features, which are either functional (i.e., SPECT/PET) voxel values or structural (i.e., MRI) voxel values. Most existing research for classifying AD/MCI cases from normal controls did not consider longitudinal data [10]. Each patient was scanned once to retrospectively determine what class the patient's imaging data belonged to. Our study is a longitudinal one whose imaging data comes from the ADNI brain database [3]. The goal of this study is to apply dimensionality reduced features to detect conversion to AD early by using SVM. We want to predict the conversion to AD before the actual conversion to AD was confirmed. A secondary goal of this study is to classify MCI and normal by using dimensionality reduced features. For early detection of AD, the SVM classifier is trained with normal and demented scans and tested for conversion patients, who converted from the normal to demented state, by only using the imaging data before the actual conversion. Existing research that had analyzed longitudinal data considered cortical features as well but did not consider dimensionality reduction with the cortical features [19]. This study builds on a previous article where dimensionality reduced cortical features were adopted for distinguishing non-longitudinal AD/MCI scans from normal controls [16]. Here, we adopt the same approach proposed but extend its application to longitudinal data to address the issue of early AD detection. The very combination of (1) using two cortical features, (2) using PCA for manifold learning, and (3) predicting early conversion to AD could not be found in existing research to the best of our knowledge. We achieved prediction accuracy of early AD conversion comparable to that in a recent study [19].

2. Materials and methods

2.1. Subjects and MRI images

Image data were obtained from the ADNI database [3]. Each subject was scanned on two or more visits, separated by at least 6 months between visits. We selected 30 normal cases, 30 MCI cases, and 12 conversion cases from the database if they were clinically classified as (1) normal controls – individuals who were cognitively normal (CDR = 0) with Mini-Mental State Examination (MMSE) scores between 28 and 30, (2) MCI – individuals with a memory complaint who experienced a very mild cognitive decline with a CDR of 0.5 and MMSE scores between 24 and 27, and (3) conversion – individuals who converted from normal to MCI. We were limited to 12 cases of conversion as there were 16 conversion cases in the database and 4 cases were deemed unsuitable for our pre-processing procedures. We randomly chose 30 normal and 30 MCI cases from the database to have adequate statistical power for each group. The MCI patients were 77.12 ± 6.83 (mean $\pm$ STD) years old and of gender ratio of 19/11 (M/F). The normal control patients were 75.13 ± 5.17 years old and of gender ratio of 18/12 (M/F). The conversion patients were 75.92 ± 5.30 years old and of gender ratio of 8/4 (M/F). All MRIs were sagittal T1-weighted scans and had typical dimensions of 256×256 and resolutions of $0.94\,\text{mm} \times 0.94\,\text{mm} \times 1.2\,\text{mm}$.

2.2. Cortical surface extraction and surface registration

We applied the same procedures described in the previous work to the longitudinal MRI data [16]. A brief summary follows. We used the MNI image processing software to produce the cortical surface and to register the extracted surfaces [20]. MR images were first registered in an affine fashion and then corrected for intensity non-uniformity. The registered and corrected volumes were then classified into white and gray matter, cerebrospinal fluid, and background. The Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm was used to extract the cortical surface [12]. A surface model for each brain hemisphere was constructed using 81,924 polygonal 3D meshes. With the extracted surface, we applied a 2D surface based non-rigid registration algorithm based on a geodesic distance from the gyral crown vertex with a smoothing term [18]. The registration software established spatial correspondence between a given image and a predefined template image, and thus all 72 images were registered onto a common template so that they could all be compared on a vertex-by-vertex basis.

2.3. Computation of cortical features

We computed two cortical features, cortical thickness and sulcal depth. The CLASP algorithm provides two cortical surfaces, the inner and the outer surface, which are deformed from a common sphere parameterized with 3D meshes. Cortical thickness was computed as the Euclidean distance between the linked vertices of the inner and the outer cortical surface. We measured the Euclidean distance from each vertex on the cortical surface to the nearest voxel on the volume of the cerebral hull as the sulcal depth [9]. We refer to the collection of features computed on the cortical surface as a feature map. The computed feature maps were resampled onto the spatial frame of the common template using the surface registration described, so that all the feature maps reside on the same spatial frame for vertex-by-vertex comparison. In summary, we obtained two features (i.e., cortical thickness and sulcal depth) defined on the common cortical surface for all 81,924 vertices for each subject. A sample of the adopted cortical features, cortical thickness and sulcal depth, is given in Fig. 1.