Neurocomputing 175 (2016) 132–145

Contents lists available at ScienceDirect

Neurocomputing

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

Multi-scale features extraction from baseline structure MRI for MCI patient classification and AD early diagnosis

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ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form
13 October 2015
Accepted 15 October 2015
Communicated by Shaoting Zhang
Available online 24 October 2015

Keywords:
Alzheimer's disease
MCI
Structural MRI
Tight wavelet frame
Multi-scale
SVM

ABSTRACT

In this study, we investigate multi-scale features extracted from baseline structural magnetic resonance imaging (MRI) for classifying patients with mild cognitive impairment (MCI), who have either converted or not converted to Alzheimer's disease (AD) three years after their baseline visit. Total 549 subjects from the Alzheimer's disease Neuroimaging Initiative (ADNI) database are included, and there are 228 Normal controls (NC), 133 MCI patients (71 of them converted to AD within 3 years, referred as MCI converters, or MCIc) and 188 AD patients. The images are preprocessed with the standard voxel-based morphometry method with segmentation of grey matter, white matter and cerebrospinal fluid. Wavelet frame, a multi-scale image representation approach, is applied to extract features of different scales and directions from the processed grey matter image data. The features are extracted for both whole grey matter images and grey matter images of the hippocampus region. The support vector machine is adopted to construct classifiers for MCIc and MCI non-converters (MCInc). The accuracy using a leave-one-out procedure for classification of AD vs. NC and MCIc vs. MCInc is 84.13% and 76.69% respectively, both achieved by local hippocampus data. Our study shows that the proposed multi-scale method is capable of discriminating MCI converters and non-converters, and it can be potentially useful for MCI prognosis in clinical applications.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease which is characterized by an initially gradual and then accelerated decline of cognitive function, and it accounts for more than half of dementia patients who cannot live alone and thus need dedicated and often long-term care. The World Alzheimer Report [40,30] indicates that the annual cost of the dementia care for the 35.6 million sufferers is around 1% of the global GDP and the number of sufferers is estimated to double in the next two decades. Meanwhile, there is no effective treatment to relieve AD, let alone a cure. Mild cognitive impairment (MCI) is a prodromal stage of AD, and approximately 10%–15% of individuals with MCI progress to AD per year [19]. At this relatively early stage, it is crucial to estimate the likelihood of conversion to AD as accurately as possible. With the development and advancement of neuroimaging techniques, there are discussions on the use of features based on such as magnetic resonance imaging (MRI) [39,15,1], fluorodeoxyglucose positron emission tomography (FDG-PET) [7,18] to estimate the conversion rate. Evidence shows that these features do provide valuable information assisting the diagnosis or prognosis with increased sensitivity and accuracy, especially in the early stages.

Compared to PET techniques, MRI is relatively inexpensive and yet performs comparably; based on numerous studies. In this study, we aim to examine the feasibility of baseline MRI to differentiate stable and convertible MCI patients using a multi-scale method that, to the best of our knowledge, is a new method for analyzing MRI data and especially in the context of AD neuroimaging studies. We first apply this multi-scale technique to extract features from preprocessed grey matter images. Then we consider two ways, namely the global approach and the hippocampus approach, to construct classifiers to distinguish MCI converters (MCIc) and MCI non-converters (MCInc) via linear support vector machine (SVM). The leave-one-out procedure is used to estimate the performance of the classifiers. Compared to various methods in the literature, the accuracy rate of our method for MCI patients is 71.43% for the global approach and 76.69% for the hippocampus approach. The p-value of the two sample t-test demonstrates that

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http://dx.doi.org/10.1016/j.neucom.2015.10.043
0925-2312/

the features of hippocampus approach have significant difference between the MCInc and MCIc samples, in line with the fact that our hippocampus feature analysis achieves a superior classification accuracy.

2. Materials and methods

Data used in this work are collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As a $60 million, 5-year public private partnership, the ADNI was launched 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. The goal of ADNI is to determine sensitive and specific AD classifiers which act as a signal of early disease and an assessment of treatment effects [27,37,38]. ADNI has long been dedicated to the investigation into the shift of the imaging biomarkers, e.g. serial magnetic resonance imaging (MRI) or positron emission tomography (PET), combined with clinical, genetic and biochemical evaluation of subjects due to the disease gradually progressing from normal to Alzheimer's Disease, especially the MCI as the transitional stage and early AD.

2.1. Subjects

This study includes 228 Normal controls (NC) samples, 133 MCI patients and 188 AD patients from one of the Standardized MRI Data Sets [43]: ADNI_1 screening 1.5T for easier comparison with other methods. We include 228 of 229 NC subjects by excluding one sample due to missing information. In MCI study, 133 samples with converted time information are investigated and among them 71 patients are converted to AD within 36 months. The demographic data of the datasets are listed in Tables 1 and 2. In the two tables, we list the p values of a two-sample t-test of *APOE4* and *MMSE Total Score* of the two groups. We can see that the two features APOE4 and MMSE both have significant differences for the NC vs. AD and the MCIc vs. MCInc group.

2.2. MRI data preprocessing

In this study, all the samples were obtained by a scanner with a standardized high-resolution MRI protocol. The size of the raw $k-$space data is $192 \times 192 \times 166$ and the size of each voxel is $1.25 \times 1.25 \times 1.2\ \mathrm{mm}^3$. For each slice along the third dimension, the image is reconstructed as 256×256 with zero-filling. Details can be found on the ADNI website.[1]

It is necessary to preprocess structural MRI data before further analysis. The preprocessed steps are performed with a widely used software SPM[2] (Statistical Parametric Mapping). We adopt a standard preprocessing procedure for MRI data. First, the VBM8 toolbox[3] in SPM8 is used to normalize T1 images in template space and to segment them into three regions: grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The segmentation algorithm involved in SPM8 is adaptive Maximum a Posterior (MAP) and Partial Volume Estimation (PVE) technique [4]. The high dimensional normalization in VBM8 adopted the registration algorithm Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL) [17]. Through all the image registration iterations and template creation, grey matter maps are normalized to their average templates and further to the Dartel template in Montreal Neurological Institute (MNI) space. Then we obtain a normalized brain image, and three segmented regions: grey matter, white matter and CSF for all subjects. For a local analysis, we use WFU Pick Atlas (http://www.nitrc.org/projects/wfu_pickatlas/) to generate region of interest (ROI) masks based on the Talairach Daemon (TD) database and other human atlases. In this study, we use the automated anatomical labeling (AAL) [35] atlas to extract the hippocampus region from the segmented grey matter images. Fig. 1 shows the flow chart of the pre-processing step. We then perform feature extraction from two groups of images: the whole grey matter image and hippocampus region masked one.

Table 1
Demographic data of NC vs. AD subjects.

Variable	NC N=228	AD N=188	p
Sex M:F	118:110	99:88	–
Age	76.0 (5.0)	75.4 (7.5)	–
APOE4	0.29 (0.5)	0.9 (0.7)	<0.001
MMSE Total Score	29.1 (1.0)	23.3 (2.0)	<0.001

Table 2
Demographic data of MCI subjects.

Variable	n MCI N=62	c MCI N=71	p
Sex M:F	44:18	45:26	–
Age	75.4 (8.0)	74.8 (7.0)	–
APOE4	0.5 (0.6)	0.8 (0.7)	0.008
MMSE Total Score	27.7 (1.6)	26.8 (1.6)	0.003

2.3. Wavelet frame

Wavelets have long time been an important tool for signal/image processing. Wavelet transforms [25,16,10] are able to extract feature in different scales from signals. For instance, Liu et al. [24] used a geometric wavelet to authenticate paintings of Van Gogh and their method achieves an accuracy of 92.19%. Hackmack et al. [20] exploited dual tree wavelet to obtain features to diagnose multiple sclerosis patients, and achieved an accuracy rate of 95.12%. Wavelet tight frames are a generalization of the standard orthogonal system, generated by translation and dilation of a wavelet function. In recent years, overcomplete wavelet frames are largely adopted in imaging applications due to their effectiveness in sparse representation and associated algorithms, see [11] for more theory and recent image applications. In this work, we are interested in exploring the multi-scale representation by wavelet frames of structural MRI data and analyzing the feasibilities of these features for AD and MCI patients classification.

Rigorously, the wavelet frame is a representation system in the image space defined in $\mathbb{R}^d$, which is often modeled as the function space $L_2(\mathbb{R}^d)$. For simplicity here, we present the definition and notation for $d=1$. Note that

$$L_2(\mathbb{R}) = \{f(x) |\ \ \|f\|_{L_{2(\mathbb{R})}} := \left(\int_{\mathbb{R}} |f(x)|^2\, \mathrm{d}x\right)^{1/2} < \infty\}.$$

Given $\Psi := \{\psi_1, \ldots, \psi_r\} \subset L_2(\mathbb{R})$ and $\psi_{l,j,k} := 2^{j/2}\psi_l(2^j \cdot -k)$, we define the wavelet system

$$X(\Psi) := \{\psi_{l,j,k} : 1 \le l \le r;\ j,k \in \mathbb{Z}\},$$

and the system $X(\Psi) \subset L_2(\mathbb{R})$ is called a tight wavelet frame of $L_2(\mathbb{R})$ if

$$\|f\|^2_{L_{2(\mathbb{R})}} = \sum_{g \in X(\Psi)} |\langle f, g\rangle|^2.$$

[1] http://adni.loni.usc.edu/methods/documents/mri-protocols/
[2] http://www.fil.ion.ucl.ac.uk/spm
[3] http://dbm.neuro.uni-jena.de/vbm8