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Ensemble of random forests One *vs.* Rest classifiers for MCI and AD prediction using ANOVA cortical and subcortical feature selection and partial least squares

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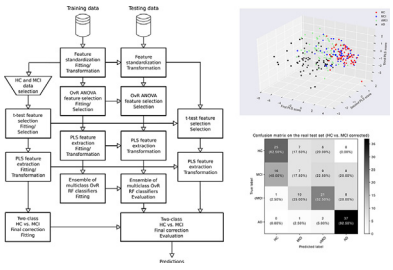
HIGHLIGHTS

- Mild cognitive impairment prediction method based on an ensemble of one *vs.* all multi-class classifier.
- Revised ANOVA feature selection method of MRI cortical and subcortical features.
- Feature dimension reduction via multi-class partial least squares.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Alzheimer's disease (AD) is the most common cause of dementia in the elderly and affects approximately 30 million individuals worldwide. Mild cognitive impairment (MCI) is very frequently a prodromal phase of AD, and existing studies have suggested that people with MCI tend to progress to AD at a rate of about 10–15% per year. However, the ability of clinicians and machine learning systems to predict AD based on MRI biomarkers at an early stage is still a challenging problem that can have a great impact in improving treatments.
Method: The proposed system, developed by the SiPBA-UGR team for this challenge, is based on feature standardization, ANOVA feature selection, partial least squares feature dimension reduction and an ensemble of One *vs.* Rest random forest classifiers. With the aim of improving its performance when discriminating healthy controls (HC) from MCI, a second binary classification level was introduced that reconsiders the HC and MCI predictions of the first level.
Results: The system was trained and evaluated on an ADNI datasets that consist of T1-weighted MRI morphological measurements from HC, stable MCI, converter MCI and AD subjects. The proposed system yields a 56.25% classification score on the test subset which consists of 160 real subjects.

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Comparison with existing method(s): The classifier yielded the best performance when compared to: (i) One *vs.* One (OvO), One *vs.* Rest (OvR) and error correcting output codes (ECOC) as strategies for reducing the multiclass classification task to multiple binary classification problems, (ii) support vector machines, gradient boosting classifier and random forest as base binary classifiers, and (iii) bagging ensemble learning.

Conclusions: A robust method has been proposed for the international challenge on MCI prediction based on MRI data. The system yielded the second best performance during the competition with an accuracy rate of 56.25% when evaluated on the real subjects of the test set.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and affects approximately 30 million individuals worldwide (Prince et al., 2013). Mild cognitive impairment (MCI) is very frequently a prodromal phase of AD, and existing studies have suggested that people with MCI tend to progress to AD at a rate of about 10–15% per year. The ability to predict AD at an early stage is still a challenging problem that can have a great impact in improvement treatments (Eskildsen et al., 2013). As the disease progresses, well defined brain areas are affected and neuropsychological clinical scores such as the Mini Mental State Examination (MMSE) and cognitive assessment subscale (ADAS-Cog) reveal cognitive decline in MCI patients (Davatzikos et al., 2011). Several previous works have attempted to identify discriminant features from T1-weighted structural magnetic resonance imaging (MRI) (Khedher et al., 2015, 2017; Martinez-Murcia et al., 2016) or from functional single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (Illán et al., 2010; Illán et al., 2011; Segovia et al., 2013; Ramírez et al., 2013), as well as robust machine learning and classification techniques (Ortiz et al., 2015; Górriz et al., 2017) for computer aided diagnosis (CAD). In other works, the aim was to develop techniques to predict whether a patient will convert from MCI to AD based on an analysis of previously collected MRI and neuropsychological clinical scores (Ortiz et al., 2017; Rodríguez et al., 2015).

Several challenges have been organized in the field of neuroimaging mainly due to the vast amount of data provided by different biomarkers that are available for analysis and prediction. The goal of the Alzheimer's disease big data DREAM challenge (https://doi.org/10.7303/syn2290704) (DREAM, 2014) was to apply an open science approach to rapidly identify accurate predictive AD biomarkers that can be used by the scientific, industrial and regulatory communities to improve AD diagnosis and treatment. DREAM provided participants with genetics data, demographics, clinical data and MR imaging collected on participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI), as well as from subsets of data from independent studies that were used to rank participants' models on the leaderboard, and as validation for final predictions (Bennett et al., 2012a,b; Lovestone et al., 2009). The challenge on Computer-Aided Diagnosis of Dementia based on structural MRI data (CADDementia, https://caddementia.grand-challenge.org) used 354 T1-weighted MRI scans with the diagnoses blinded. The best performing algorithm yielded an accuracy of 63.0% and an area under the receiver-operating-characteristic curve (AUC) of 78.8%. In general, the best performances were achieved using feature extraction based on voxel-based morphometry or a combination of features that included volume, cortical thickness, shape and intensity (Bron et al., 2015). The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge (https://tadpole.grand-challenge.org/) is an ongoing challenge organized by the EuroPOND consortium in collaboration with ADNI. The object of the challenge is to predict who will develop clinical, cognitive, and MRI signs of disease in a short enough timeframe to carry out a clinical trial. Prediction models will be tested on existing data (cognitive tests, MRI, positron emission tomography of amyloid and glucose metabolism, and cerebrospinal fluid biomarkers) that has been collected in ADNI1, ADNI-GO, and ADNI2 on cognitively normal people and others with mild cognitive impairment.

The present International challenge for automated prediction of MCI from MRI data, organized by Alessia Sarica, Antonio Cerasa, Aldo Quattrone and Vince Calhoun, was developed in order to let the participants compare the vast series of machine learning algorithms and predictive markers on the same training and test sets. Pre-processed sets of T1-weighted MRI from stable AD patients, individuals with MCI who converted to AD, individuals with MCI who did not convert to AD and healthy controls were provided to participants in the challenges. MRIs matched for sequence characteristics (i.e. MPRAGE) and analyzed using FreeSurfer v.5.3 were provided by ADNI. The feature space consists of cortical thickness and subcortical volumes, hippocampal subfields included, since previous studies demonstrated the reliability of these morphological measurements for improving automated diagnosis of AD (Desikan et al., 2009; de Vos et al., 2016; Vasta et al., 2016). This paper shows the system developed by the Signal Processing and Biomedical Applications (SiPBA) research group from the University of Granada (SiPBA-UGR Team) for the International challenge on automated prediction of MCI from MRI data. The aim is to develop a robust method to improve early AD detection that would provide opportunities for early intervention, symptomatic treatment, and improved patient function. Thus, special attention is paid to MCI subjects and their conversion to AD.

2. Materials and methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.1. Datasets

This section shows the datasets that were provided for the International challenge for automated prediction of MCI from MRI data (https://inclass.kaggle.com/c/mci-prediction). MRIs were selected from the Alzheimer's disease Neuroimaging Initiative (ADNI, http://www.adni-info.org) and preprocessed by Freesurfer (v5.3) (Fischl, 2012; Fischl and Dale, 2000). In total 429 demographical, clinical as well as cortical and subcortical MRI features were available for each subject.

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