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Predictive Modeling Of Alzheimer's Disease Prognosis Using Anatomical & Diffusion MRI

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Abstract

Mild cognitive impairment (MCI) is an intermediate stage between healthy aging and Alzheimer's disease (AD), and AD is a progressive neurodegenerative disorder that affects around 50 million people worldwide. As new AD treatments begin to be developed, one key goal of AD research is to predict which individuals with MCI are most likely to progress to AD over a given interval (such as 2 years); if successful, these individuals could be preferentially enrolled in drug trials that aim to slow AD progression. Here we benchmarked a range of MCI-to-AD predictive models including linear regressions, support vector machines, and random forests, using predictors from anatomical and diffusion-weighted brain MRI, age, sex, APOE genotype and standardized clinical scores. In evaluations on 2,448 subjects (1,132 MCI, 883 healthy controls, 433 with dementia) from the ADNI study, models including PCA-compacted features achieved a balanced accuracy of 75.3% (using cortical features) and 89.7% using diffusion MRI measures on test set, suggesting the added prognostic value of microstructural metrics obtainable with diffusion MRI.

Index-Terms: Alzheimer's disease, diffusion tensor imaging, MRI, prognosis, machine learning

1. Introduction

Alzheimer's disease (AD) is a chronic, progressive and irreversible neurodegenerative disorder [1] that affects around 50 million people worldwide. It is characterized by a decline in memory and other cognitive functions. By the year 2050, it is estimated that around 30 million new cases will be reported per year [2]. As new anti-amyloid treatments are only just becoming available for AD, early diagnosis and prognosis of AD is of the utmost importance.

MCI (mild cognitive impairment) is a prodromal form of AD, characterized by mild symptoms of brain dysfunction. People with MCI can typically perform daily activities but are more prone to developing dementia eventually [4,5]. People with MCI progress to AD at an annual rate of 10-15%; approximately 80% of them will have converted to AD after six years. There is considerable interest in discovering biomarkers from clinical, neuroimaging and genetic data that can help to predict which MCI subjects will decline to AD [6-7].

Among the measures that have been associated with faster progression from MCI to AD are: (1) baseline clinical scores on standardized tests such as the ADAS-Cog, MMSE, and the clinical dementia rating (CDR), (2) abnormal accumulation of beta-amyloid and tau proteins in the brain or CSF, (3) abnormalities in MRI morphometric measures such as hippocampal volumes, regional cortical volumes or regional cortical thickness, and (4) diffusion MRI metrics that examine white matter microstructure; the latter have also been found to be correlated with clinical dementia ratings, and with brain amyloid load [2].

The recent AT(N) framework [8] for subtyping of dementia highlights the value of measuring accumulated amyloid and tau proteins in the brain or cerebrospinal fluid (CSF), but the high cost, invasiveness, and limited availability of PET scans, and the invasiveness of lumbar puncture to measure spinal CSF, has led to interest in predicting decline from MRI-based imaging metrics [3]. Finally, some predictive models have used blood and fluid-based biomarkers, as well as genotyping for the APOE4 risk allele, which increases a person's lifetime risk of late-onset AD by a factor of roughly 3 per allele carried, depending on their ancestry. Of all these biomarkers and predictors, a method is needed to rank their added value, to create a simple prognostic model of AD prognosis.

Many studies have tested machine learning or deep learning for diagnostic classification and for predicting future progression from MCI to AD using various biomarkers. Wolz et al. [9] used support vector machines (SVM) and linear discriminant analysis (LDA) to analyze conversion of sMCI (stable MCI), pMCI (progressive MCI) or HC (healthy controls) to AD based on data from 834 participants in the ADNI study. Cheng et al. [10] used domain transfer learning and SVM on ADNI

(N=202) and predicted MCI-to-AD conversion with 79.4% balanced accuracy using derived measures from MRI, PET, and CSF. Ewers et al. [11] achieved prediction accuracy of 64.6% for MCI to AD conversion based on CSF and neuropsychological tests in 182 ADNI participants.

Zhang et al. [12] proposed multi-modal multi-task (M3T) learning where they used the correlations in the information available from MRI, CSF data, and FDG-PET. Using SVM, they regressed values for MMSE and ADAS-cog test scores and classified subjects into multiple conversion categories with 73.9% accuracy. Wee et al. [13] studied correlations between various cortical measures using similarity maps. Using SVM, they achieved 92.4% accuracy for AD classification with an AUC-ROC of 0.974; they achieved 75.1% accuracy (AUC-ROC, 0.843) for predicting which MCI subjects converted to AD.

Based on the above studies, we set out to benchmark methods for MCI-to-AD conversion based on: (1) classical machine learning methods that work on tabular data, (2) clinical, demographic, genetic, and anatomical and diffusion MRI measures, and PCA-based compactions of these measures. Given the empirical correlations between demographic and genetic information, neuropsychological assessments, gray matter features extracted from MRI, and various dMRI measures, we extracted new features based on the correlations between these features and studied their predictive accuracy. We aimed to define the added value of the imaging metrics, and in particular diffusion MRI, which can add a novel metric of white matter microstructure not available using standard T1-weighted anatomical MRI.

2. Method

2.1. Dataset Description

We included data from all phases of the Alzheimer's Disease Neuroimaging Initiative [14] (ADNI1, ADNI2, ADNI3, and ADNI-GO). ADNI is a multisite North American study that evaluates various biomarkers of AD from multiple neuroimaging modalities; molecular and clinical biomarkers, genetic information, demographics, and neuropsychological assessments of AD. A key goal of ADNI is to identify biological markers that are sensitive to the clinical progression of AD. Progression is evaluated using clinical assessments at regular intervals, including baseline, 3 month, 6-, 12-, 24-months and later assessments.

For this study, a total of 2,448 subjects (1,132 with MCI, 883 healthy controls, and 433 with dementia) from ADNI were included (1,161 females, 1,287 males).

In the predictor set for MCI-to-AD conversion, we considered a range of readily and less readily available features including age at the initial scan, sex, number of APOE4 alleles, and results of standardized clinical tests including the MMSE, sum-of-boxes clinical dementia rating (CDR-SB), ADAS11 and ADAS13. These features are called *raw data* in this study. The subjects throughout ADNI phases are classified as controls, MCI or AD at baseline and at 2 year follow-up. Later, models were trained to detect which baseline MCI subjects had progressed to AD in a span of 2 years after their baseline assessment.

We started our analysis with the *raw data* and analyzed the performance of the model. Later, gray matter volumes of cortical regions extracted from T1-weighted MRI scans using FreeSurfer were added. These features consisted of gray matter volumes for regions such as the caudal anterior cingulate, caudal middle frontal gyrus, cuneus, entorhinal cortex, and fusiform gyrus.

We also studied the performance of four dMRI measures extracted from a set of candidate regions of interest in the ADNI3 dataset. The four indices measured were standard diffusion tensor indices: fractional anisotropy (FA), and mean (MD), radial (RD) and axial diffusivity (AxD). The considered white matter regions were the fornix/stria terminalis (Fx/St), cingulum (CGH), uncinate fasciculus (UNC), genus of corpus callosum (GCC), and full white matter (FWM). These features were selected based on multiple prior studies indicating their association with AD [15]. To avoid circularity and data leakage, we only included ADNI3 data for the DTI evaluations, as the selection of promising DTI features was partly based on their association with AD and with clinical dementia ratings in ADNI2.

2.2 Algorithms Tested

We employed classical machine learning algorithms including support vector machines (SVMs), K-Nearest Neighbors (KNN), random forests (RF), and linear regression (LR) to classify subjects into various categories. Principal components analysis (PCA) was used to capture the variance and correlation among the features considered. We generated new features using PCA and combined them with the *raw data* for further analysis.

2.3. Method

The following algorithm was followed in the proposed work:

1. Collaboration of *raw data* (Sex, Age, number of APOE alleles, test score values on the MMSE, CDR-SB, ADAS11, ADAS13) across all phases of ADNI.
2. Computation of gray matter metrics and quality checking them.
3. Collection of previously specified dMRI features for ADNI 3 subjects.
4. Finding null values and imputing them with the median value of the group that the person belongs to.
5. Encoding of string values using Label Encoder.
6. Feature extraction using PCA and checking the variance explained by the first principal component.
7. Merging features (cortical or dMRI) with raw data and newly extracted features.
8. Resampling of entire data by oversampling the under-represented class and rescaling of the entire data. Division of dataset in a 7:2:1 ratio for training, testing, and validation.
9. Training models with 70% of data and fine-tuning using 10% of the total dataset.
10. Analyzing performance of the fine-tuned models with the test data (20% of the total).

We examined two types of progression in this study: from MCI to AD during a span of two years, and the related task of predicting progression of healthy controls to MCI or AD over a 2-year interval after their first scan. As inputs, we used PCA to calculate correlation between features in the following combinations:

- Only *Raw data* (Sex, Age, number of APOE alleles, test score values on the MMSE, CDR-SB, ADAS11, ADAS13)
- *Raw data* with cortical features extracted using FreeSurfer [16].
- *Raw data* with the 4 dMRI measures (AxD, FA, MD, RD) from 5 regions of interest.

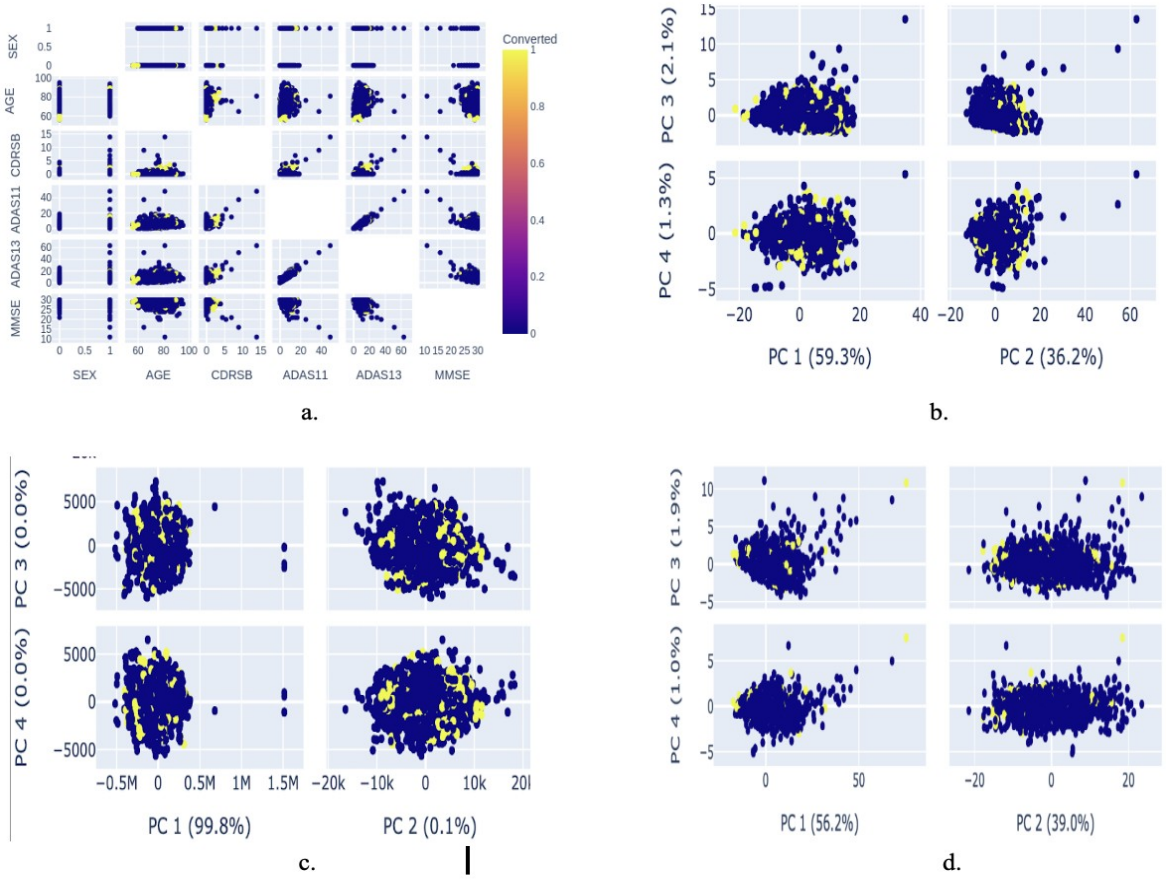

Figure 1. a. Correlations are visualized between different pairs of features in the raw data, **b.** Shows PCA results for only the raw data, **c.** depicts the results when cortical region gray matter volumes were included, **d**. shows the results obtained from a combination of dMRI measures with raw data.

3. Results and Discussion

The performance of the above-mentioned models was analyzed based on parameters including overall and balanced accuracy, area under the receiver operating characteristic curve (AUC-ROC), and F1 scores, with 10-cross validation. Figure 1 displays the results for PCA analysis where points colored yellow represent "Converted" subjects(MCI->AD) whereas points in blue color represent "Non-converted" subjects. **Figure 1(a)** displays the correlations in the *raw data* using PCA. The first principal component accounts for only 59.3% of the variance in this input data, as shown in **Figure 1b.** When the *raw data* is combined with cortical features for predicting controls to MCI/AD conversion, the first principal component of the input data accounts for 99.8% of the variance. PC one explained 59.3% of the variance in MCI to AD conversion. Combining *raw data* with dMRI features explained 56.2% of the input variance in control to MCI/AD conversion and 64.1% of the input variance in MCI to AD conversion on ADNI 3 data.

Overall, we predicted MCI to AD conversions over a span of two years, with 75.5% balanced accuracy using cortical measures and 89.4% using dMRI measures. For the related task of predicting Controls to AD/MCI conversion across all ADNI datasets, we achieved 96.9% balanced accuracy with cortical features, and 96.4% when using dMRI measures in the ADNI 3 dataset.

4. Conclusion

To the best of our knowledge, the proposed method outperforms many prior works on this task. **Figure 1** shows how correlated the features are, suggesting the value of including cortical regional gray matter volume and dMRI measures to calculate new PC features.

Limitations of this study include the lack of consideration of more invasive biomarkers (tau and amyloid), and blood and biofluid assessments. This information was omitted due to limited information on these measures in the initial ADNI phases. In future, it will be valuable to study the added value of these ancillary markers. Even so, these initial benchmarks show the promise of predicting AD progression from a simple set of baseline biomarkers.

5. Compliance with Ethical Standards

All ADNI data are publicly available.

6. Acknowledgments

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Predictive Task	Input Features	Best Performing Classifier	Dataset	Results
Controls→MCI/AD	Raw data	RF	All ADNI	ROC: 0.926 Balanced accuracy: 92.6% F1 score: 93.1%
Controls→MCI/AD	Raw data + cortical	RF	All ADNI	ROC: 0.954 **Balanced accuracy: 96.9%** F1 score: 95.4%
MCI→AD	Raw data + cortical	SVM	All ADNI	ROC: 0.783 Balanced accuracy:75.5% F1 score: 70.1%
Controls→MCI/AD	Raw data + dMRI	KNN	ADNI 3	ROC: 0.957 Balanced accuracy: 96.4% F1 score: 96.0%
MCI→AD	Raw data + dMRI	RF	ADNI 3	ROC: 0.901 **Balanced accuracy: 89.4%** F1 score: 88.8%

Table 1. Predictive Accuracy for MCI to AD conversion and Control to MCI/AD conversion, noting the dataset used, features employed for PCA. Also the best performing classifier is noted for each task.

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