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Multimodal prediction of conversion to Alzheimer's disease based on incomplete biomarkers*

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Abstract

Background: This study investigates the prediction of mild cognitive impairment-to-Alzheimer's disease (MCI-to-AD) conversion based on extensive multimodal data with varying degrees of missing values.

Methods: Based on Alzheimer's Disease Neuroimaging Initiative data from MCI-patients including all available modalities, we predicted the conversion to AD within 3 years. Different ways of replacing missing data in combination with different classification algorithms are compared. The performance was evaluated on features prioritized by experts and automatically selected features.

Results: The conversion to AD could be predicted with a maximal accuracy of 73% using support vector machines and features chosen by experts. Among data modalities, neuropsychological, magnetic resonance imaging, and positron emission tomography data were most informative. The best single feature was the functional activities questionnaire.

Conclusion: Extensive multimodal and incomplete data can be adequately handled by a combination of missing data substitution, feature selection, and classification.

Keywords: Mild cognitive impairment; Alzheimer's dementia; Prognosis; Multimodal biomarker; Missing data; Feature selection

1. Background

Alzheimer's disease (AD) is the most common cause for dementia in the elderly and primarily diagnosed based on clinical symptoms such as memory loss and disorientation [1]. As an intermediate stage between normal age-related cognitive decline and dementia, mild cognitive impairment (MCI) has been identified [2]. Because not all MCI patients convert to AD and the MCI group is very heterogeneous, it is a highly relevant task to differentiate MCI subjects who will develop AD within the next years from those who will be stable or even improve.

Recent studies tried to solve this task by using a combination of biomarkers, e.g. obtained via positron emission tomography (PET) or magnetic resonance imaging (MRI), and algorithms adopted from machine learning [3–5]. Computer-based decision support systems are assumed to be not only more sensitive for the detection of early disease states, but also more objective and reliable than medical decisions made by single clinicians [6]. Those automatic diagnostic tools become especially important when data of different modalities are integrated into one diagnostic decision as recommended by the National Institute on Aging

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(NIA), because this requires expertise in more than one clinical field.

In this study we consider several generalizations with the aim (1) to make full use of databases such as the ADNI (Alzheimer's Disease Neuroimaging Initiative [7]) and (2) to optimize automatic multimodal classification for use in everyday clinical routine.

First, what is a good way to deal with missing data? Missing data are a severe problem in many medical databases and is usually solved by discarding all patients with missing data. However, for multimodal data it is very likely that most of the patients will lack data from one or the other domain and a requirement of complete cases results in very small data sets. Here, we compared three different approaches to replace ("impute") missing data entries: mean imputation, imputation by the Expectation-Maximization (EM) algorithm, and a combined approach.

Second, most studies focus on a certain subset of domains for automatic multimodal classification (e.g., neuropsychology and MRI), not least because of missing data [4,8–10]. By replacing missing values, we were able to take the multimodal approach further and include all modalities available in ADNI. In total we assessed 288 features from 10 different domains including clinical data, neuropsychology, genetics, biospecimen, MRI, and PET.

Third, if expert knowledge is not yet available or not yet complete, it is desirable to have a framework that can deal with features of different importance and even irrelevant features, namely by automatic feature selection. Here, we compared two methods for fully automatic feature selection (F-score and feedforward/backward selection) with manual feature selection by a group of experts.

Fourth, we compared three state-of-the-art classification algorithms: Support Vector Machines (SVMs), a single classification tree, and Random Forests. By not making any concrete assumptions about the scale or the distribution of the data, they are well suited for the analysis of data sets comprising many different features.

Fifth, what is a good way to deal with unbalanced data? Class frequency is often unbalanced and can lead to large discrepancies between sensitivity and specificity [8]. Here, we propose a way to balance sensitivity and specificity via the receiver operating characteristic (ROC).

2. Methods

2.1. Data

2.1.1. Subjects

Data used in this project were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was initiated in 2003 by the NIA, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration, pharmaceutical companies, and nonprofit organizations for the development of diverse biomarkers for the early detection of AD [7] (For more information on study procedures see http://adni.loni.usc.edu/methods/documents/).

For this study, patients with a baseline diagnosis of MCI and a follow-up time of at least 36 months were extracted from the ADNI database. Patients who were diagnosed with MCI, NL or MCI to NL at all visits during the 3-year follow-up were included in the MCI-stable group, whereas patients whose diagnosis changed to AD during the 3-year follow-up were regarded as MCI-converters. After this procedure, 237 patients were selected, 151 of which belonged to the MCI-stable group, and 86 to the MCI-converter group (see Table 1).

2.1.2. Features

Based on the ADNI database, features from 10 modalities were extracted including neuropsychological testing (NP, 15 features), medical history (MEDHIST, 21 features), medical symptoms at baseline (BLSYMP, 25 features), neurological and physical examinations (EXAMS, 28 features), MRI lesion load (LESION, 1 feature), MRI volume-based morphometry (VOLUME, 24 features), voxel-based morphometry (VOXEL, 117 features), laboratory data including cerebrospinal fluid (CSF) examinations (BIO, 47 features), PET scans (PET, 7 features), and demographic information about age, gender, and education (DEMO, 3 features). This resulted in a total of 288 features (see Table B.4). All features were obtained from the baseline visits of the patients.

Please note that we here only used the sum scores of the different neuropsychological tests because we assumed that they cover all important aspects of the test. However, because it might be also interesting to look at specific domains of cognition, we performed additional analyses on the subscores of the Alzheimer's Disease Assessment Score (ADAS) and the functional activities questionnaire (FAQ).

In our final feature set, 7.94% of data were missing (9.1% in the MCI-stable group and 5.9% in the MCI-converter group). The number of missing values per feature varied between 0% and 82.12% for MCI-stable patients

Table 1
Baseline subject characteristics

Characteristic	MCI-stable (n = 151)	MCI-converters (n = 86)	*P*-value
Age, mean (SD)	74.12 (7.66)	74.62 (6.90)	.61
Gender			.76
Females, n (%)	48 (31.79)	29 (33.72)	
Males, n (%)	103 (68.21)	57 (66.28)	
Education, y; mean (SD)	15.82 (2.96)	15.72 (3.02)	.80
MMSE, score; mean (SD)	27.59 (1.69)	26.69 (1.72)	1.1×10^{-4}

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation; y, years; MMSE, Mini-Mental State Examinations.

NOTE. *P*-values were calculated via a two-sided *t*-test. For baseline characteristics of other features, see Table B.4.