Journal of Neuroscience Methods 256 (2015) 168–183

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Clinical Neuroscience

Effects of imaging modalities, brain atlases and feature selection on prediction of Alzheimer's disease

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HIGHLIGHTS

- We investigate imaging-based prediction of conversion from MCI to AD.
- We compare unimodal and multimodal features from MRI, FDG-PET and their combinations.
- Multimodal features are found to be better than unimodal features to predict AD.
- FDG-PET is found to be better than MRI, particularly when using AAL-based features.
- SVM-RFE can improve the predictive accuracy when using atlas-based imaging features.

ARTICLE INFO

Article history:
Received 26 January 2015
Received in revised form 27 July 2015
Accepted 18 August 2015
Available online 28 August 2015

Keywords:
Alzheimer's disease
Mild cognitive impairment
^{18}F-fluorodeoxyglucose positron emission tomography
Magnetic resonance imaging
Support vector machine
Feature selection

ABSTRACT

Background: The choice of biomarkers for early detection of Alzheimer's disease (AD) is important for improving the accuracy of imaging-based prediction of conversion from mild cognitive impairment (MCI) to AD. The primary goal of this study was to assess the effects of imaging modalities and brain atlases on prediction. We also investigated the influence of support vector machine recursive feature elimination (SVM-RFE) on predictive performance.

Methods: Eighty individuals with amnestic MCI [40 developed AD within 3 years] underwent structural magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans at baseline. Using Automated Anatomical Labeling (AAL) and LONI Probabilistic Brain Atlas (LPBA40), we extracted features representing gray matter density and relative cerebral metabolic rate for glucose in each region of interest from the baseline MRI and FDG-PET data, respectively. We used linear SVM ensemble with bagging and computed the area under the receiver operating characteristic curve (AUC) as a measure of classification performance. We performed multiple SVM-RFE to compute feature ranking. We performed analysis of variance on the mean AUCs for eight feature sets.

Abbreviations: AAL, Automated Anatomical Labeling; Aβ, amyloid-β; AD, Alzheimer's disease; ADAS-J cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale Japanese version; ADNI, Alzheimer's Disease Neuroimaging Initiative; aMCI, amnestic mild cognitive impairment; ANCOVA, analysis of covariance; ANOVA, analysis of variance; AUC, area under the curve; CMRglc, cerebral metabolic rate for glucose; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; GDS, Geriatric Depression Scale; GM, gray matter; LOOCV, leave-one-out cross-validation; LPBA40, LONI Probabilistic Brain Atlas; MCI, mild cognitive impairment; MCI-C, MCI converter; MCI-NC, MCI nonconverter; MMSE, Mini-Mental State Examination; MR, magnetic resonance; MRI, magnetic resonance imaging; MSVM-RFE, multiple support vector machine recursive feature elimination; NFT, neurofibrillary tangle; PVE, partial volume effects; RFE, recursive feature elimination; ROC, receiver operating characteristic; ROI, region of interest; SEAD-J, Studies on Diagnosis of Early Alzheimer's Disease-Japan; SVM, support vector machine; VBM, voxel-based morphometry; WMH, white matter hyperintensity; WMS-R-LM, Wechsler Memory Scale-Revised Logical memory test.

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[1] Data used in the preparation of this article were obtained from the Research group of the Studies on Diagnosis of Early Alzheimer's Disease-Japan (SEAD-J), which comprised investigators from nine different facilities. As such, the investigators within the SEAD-J study group contributed to the design and implementation of SEAD-J and/or provided data but did not participate in the analysis or writing of this report.

[2] 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.

http://dx.doi.org/10.1016/j.jneumeth.2015.08.020
0165-0270/

Results: The interactions between atlas and modality choices were significant. The main effect of SVM-RFE was significant, but the interactions with the other factors were not significant.
Comparison with existing method: Multimodal features were found to be better than unimodal features to predict AD. FDG-PET was found to be better than MRI.
Conclusions: Imaging modalities and brain atlases interact with each other and affect prediction. SVM-RFE can improve the predictive accuracy when using atlas-based features.

1. Introduction

Alzheimer's disease (AD), which is the main cause of dementia, is a slowly progressive neurodegenerative disorder that leads to declines in memory and other cognitive abilities (Alzheimer's Association, 2013). The revised diagnostic criteria and guidelines for AD (Jack et al., 2011) proposed three stages of AD, including preclinical AD (Sperling et al., 2011), mild cognitive dementia (MCI) due to AD (Albert et al., 2011), and dementia due to AD (McKhann et al., 2011). MCI is a heterogeneous clinical entity that pertains to characteristics between those associated with normal aging and AD, and some individuals with MCI develop AD later (Petersen et al., 1999, 2001).

Among the neuropathological hallmarks of AD, neurofibrillary tangles (NFTs), and senile plaques are considered essential for neuropathological diagnosis of AD (Hyman et al., 2012). NFTs are, at least initially, intraneuronal fibrils primarily composed of hyperphosphorylated tau protein, whereas senile plaques are extracellular deposits of amyloid-β (Aβ) peptides. Progression of these AD neuropathological changes probably begins decades before the onset of cognitive decline (Mufson et al., 2012). Early detection of AD is, therefore, important as a basis for early intervention with disease-modifying drugs (Giacobini and Gold, 2013).

Three imaging biomarkers, as biomarkers to identify brain changes that precede the earliest symptoms, are included in the research criteria for diagnosis of MCI due to AD (Albert et al., 2011). Positron emission tomography (PET) amyloid imaging can measure and visualize Aβ deposition. Hippocampal volume or medial temporal atrophy on magnetic resonance imaging (MRI) and brain glucose hypometabolism on ^{18}F-fluorodeoxyglucose (FDG)-PET imaging are measures reflecting neuronal injury, namely, general damage to neurons and synapses (Jack and Holtzman, 2013). Besides structural MRI and FDG-PET, imaging techniques reflecting neuronal injury include single photon emission tomography (SPECT) perfusion imaging (Ito et al., 2013), diffusion tensor imaging (DTI) (Oishi et al., 2011), functional MRI (fMRI) (Li et al., 2015), and MRI perfusion (Chao et al., 2010). Among these, available data for MRI-related biomarkers except structural MRI are limited and less validated. These neuronal injury markers on MRI or FDG-PET are considered to be less direct or nonspecific evidence of AD, not direct evidence of the presence of Aβ or tau (Albert et al., 2011).

However, these markers are considered to be associated with synaptic loss, which is one of the major neuropathological findings in the brains of individuals with early AD (Scheff et al., 2006). Synaptic loss and neuronal loss are the major pathological substrates of cortical atrophy (Serrano-Pozo et al., 2011) and correlates with cognitive decline (Terry et al., 1991). Longitudinal progression of cognitive decline correlates brain glucose metabolic changes (Shokouhi et al., 2013). Synaptic loss occurs in the limbic regions and the neocortex in individuals with amnestic MCI (aMCI) (Scheff and Price, 2006). Different from the distribution of Aβ deposition, temporospatial accumulation of NFTs originates in the entorhinal cortex constituting the anterior portion of the parahippocampal gyrus and extends through the limbic regions to the neocortex (Braak and Braak, 1991).

Structural MRI and FDG-PET are topographical biomarkers that can help to characterize clinical subtypes with distinct regional patterns of cortical hypometabolism in FDG-PET and of cortical atrophy on structural MRI. FDG-PET has good sensitivity in detection of early brain dysfunction in AD among topographical markers (Dubois et al., 2014). In addition, structural MRI and FDG-PET are less invasive than CSF biomarkers and less expensive than Amyloid PET imaging. On the basis of these foundations, MRI and FDG-PET, particularly their multimodal combination (Price, 2012), can provide valuable biomarkers for early detection of AD. FDG-PET abnormalities are known to precede any cognitive symptoms in individuals who later develop AD (Jack et al., 2010). However, the relative diagnostic abilities of MRI and FDG-PET and of combinations of these different modalities for early disease detection remain controversial (Karow et al., 2010; Mosconi et al., 2006). To achieve scientific evidence of the diagnostic utility of FDG-PET and of MRI in early diagnosis of AD, the Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) (Kawashima et al., 2012) was launched in 2005 along with other multicenter clinical trials.

Predictive models based on machine learning algorithms have been widely used for MCI classification (Cuingnet et al., 2011; Young et al., 2013; Zhang et al., 2011). The choice of distinguishing features has an important role in pattern classification (Duda et al., 2001). Atlas-based parcellation using a predefined anatomical brain atlas is a simple feature extraction method with good interpretability and general versatility (Cuingnet et al., 2011; Zhang et al., 2011). Because of the brain atlas concordance problem (Bohland et al., 2009), the use of different brain atlases for parcellation provides different features and can affect the ability to predict conversion from MCI to AD. We have recently reported the importance of the choice of brain atlases for feature extraction in the prediction of conversion by using atlas-based MR biomarkers (Ota et al., 2014). Differences in imaging modalities can also affect predictive performance. However, the effects of imaging modalities and brain atlases for feature extraction on AD prediction have not been well documented.

In addition to feature extraction, feature selection is also important in view of dimension reduction for improving generalization ability and identifying distinguishing features. The effects of feature selection on AD predictive performance remain controversial (Chu et al., 2012; Cuingnet et al., 2011; Kerr et al., 2014). Our previous results (Ota et al., 2014) for MR-based features suggest that support vector machine (SVM)-based recursive feature elimination (RFE) can be important in AD prediction. However, the effects of the use of FDG-PET features or multimodal combination of MRI and FDG-PET features on feature selection have not been clarified.

The primary goal of this study was to assess the effects of imaging modalities and of brain atlases and their interactions on AD prediction. We performed atlas-based feature extraction from MRI and FDG-PET data by using different brain atlases. Using these unimodal or multimodal imaging feature sets, we performed SVM-based classification of MCI and added SVM-RFE feature selection to also evaluate the influence of feature selection on the classification performance.