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A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages

Saima Rathore[a], Mohamad Habes[a], Muhammad Aksam Iftikhar[b], Amanda Shacklett[a], Christos Davatzikos[a,*]

[a] Center for Biomedical Image Computing and Analytics, Perelman School of Medicine, University of Pennsylvania, USA
[b] Department of Computer Science, Comsats Institute of Information technology, Lahore, Pakistan

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ABSTRACT

Neuroimaging has made it possible to measure pathological brain changes associated with Alzheimer's disease (AD) in vivo. Over the past decade, these measures have been increasingly integrated into imaging signatures of AD by means of classification frameworks, offering promising tools for individualized diagnosis and prognosis. We reviewed neuroimaging-based studies for AD and mild cognitive impairment classification, selected after online database searches in Google Scholar and PubMed (January, 1985–June, 2016). We categorized these studies based on the following neuroimaging modalities (and sub-categorized based on features extracted as a post-processing step from these modalities): i) structural magnetic resonance imaging [MRI] (tissue density, cortical surface, and hippocampal measurements), ii) functional MRI (functional coherence of different brain regions, and the strength of the functional connectivity), iii) diffusion tensor imaging (patterns along the white matter fibers), iv) fluorodeoxyglucose positron emission tomography (FDG-PET) (metabolic rate of cerebral glucose), and v) amyloid-PET (amyloid burden). The studies reviewed indicate that the classification frameworks formulated on the basis of these features show promise for individualized diagnosis and prediction of clinical progression. Finally, we provided a detailed account of AD classification challenges and addressed some future research directions.

Introduction

Alzheimer's disease (AD), the most prevalent form of dementia, is expected to affect 1 out of 85 people in the world by the year 2050 (Brookmeyer et al., 2007). The pathophysiology of AD is increasingly becoming clearer. The brain of an AD patient accumulates abnormal proteins (Aβ and tau) in the form of amyloid *plaques* and neurofibrillary tangles, eventually resulting in loss of neurons (Frisoni et al., 2010; Jagust, 2013). Brain changes due to AD occur even before amnestic symptoms appear (Buckner, 2004), and occur in a pattern that typically includes the temporal lobe and hippocampus (Braak and Braak, 1991). It has been suggested that this inevitable atrophy can be a valuable marker of neurodegeneration (Frisoni et al., 2010), as measured with structural magnetic resonance imaging (sMRI). Further alterations in function, connectivity and metabolism can be detected using functional MRI (fMRI) (Agosta et al., 2012; Binnewijzend et al., 2012; Dennis and Thompson, 2014; Fan et al., 2011; Fox and Raichle, 2007), and fluorodeoxyglucose positron-emission tomography (FDG-PET) (Gray et al., 2012; Padilla et al., 2012; Pagani et al., 2015; Teipel et al., 2015; Toussaint et al., 2012). However, the subtleties of the changes in early AD stages make it difficult to distinguish patterns easily by conventional radiologic readings or even by quantitative analysis. Thus, it remains challenging to establish reliable markers for diagnosing and monitoring disease progression in the early stages and on an individual basis.

Numerous neuroimaging studies have used region of interest

Abbreviations: AAL, Automated anatomical labeling; AD, Alzheimer's disease; ADNI, Alzheimer's disease neuroimage initiative; AUC, Area under a receiver-operating-characteristic curve; CN, Cognitively normal; CSF, Cerebrospinal fluid; DMAF, Density maps as features; DMN, Default mode network; DTI, Diffusion tensor imaging; FDG-PET, Fluorodeoxyglucose positron emission tomography; fMRI, Functional magnetic resonance imaging; GM, Gray matter; LDA, Linear discriminant analysis; LPBM, Linear program boosting method; LR, Logistic regression; MCI, Mild cognitive impairment; MRI, Magnetic resonance imaging; mRMR, Minimum-redundancy and maximum-relevance; OASIS, Open access series of imaging initiatives; pMCI, Progressive mild cognitive impairment; RAVENS, Regional analysis of volumes examined in normalized space; ROI, Region of interest; RLR, Regularized logistic regression; RVM, Relevance vector machines; rs-fMRI, Resting state functional magnetic resonance imaging; sMCI, Stable mild cognitive impairment; sMRI, Structural magnetic resonance imaging; SPARE-AD, Spatial pattern of abnormality for recognition of early Alzheimer's disease; SVM, Support vector machines; SVM-RFE, Support vector machines-recursive feature elimination; VAF, Voxels as features; VBM, Voxel based morphometry; WM, White matter

* Correspondence to: Center for Biomedical Image Computing and Analytics, University of Pennsylvania, 3700 Hamilton Walk, Philadelphia, PA 19104, USA.
E-mail address: christos.davatzikos@uphs.upenn.edu (C. Davatzikos).

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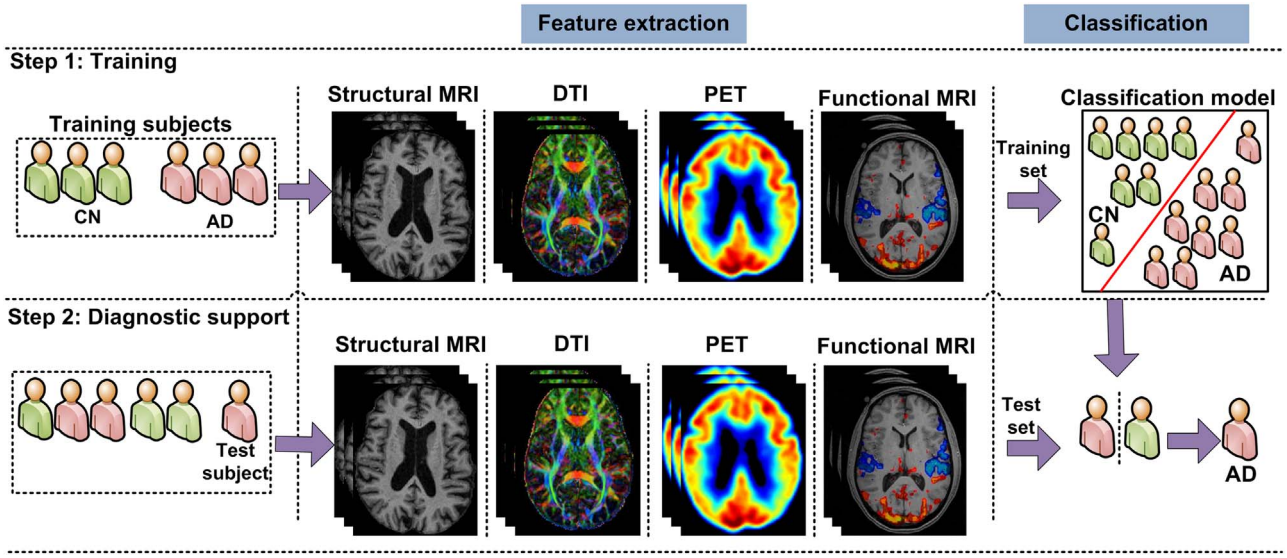

Fig. 1. A top-level layout of neuroimaging-based classification framework for AD classification.

(ROI)-types of analyses to investigate subtle changes associated with AD (Chetelat and Baron, 2003; Lerch et al., 2008). Such studies rely solely on prior knowledge to guide the selection of ROIs and features, thus ignoring brain changes outside the studied region(s) and failing to discover new knowledge. Machine learning offers a systematic approach in developing sophisticated, automatic, and objective classification frameworks for analyzing high-dimensional data and can learn complex and subtle patterns of change across various imaging modalities (Sajda, 2006). Typically, a classification framework includes atleast feature extraction and classification algorithm to build predictive models that facilitate the automation of medical decision support (Chiang and Pao, 2016) and provide increased objectivity in these decisions. Furthermore, classification frameworks can be used to develop imaging markers or indices (Davatzikos et al., 2008) with high sensitivity and specificity in individuals (Sajda, 2006) that can summarize the imaging profile of a subject into a single meaningful value (Habes et al., 2016b). This creates a more individualized, patient-tailored approach (Ithapu et al., 2015), which is imperative in the current age of personalized medicine because it allows further consideration of genetic or life-style risks, by utilizing advanced computational power (Habes et al., 2016a, 2016b, 2016c).

In recent years, a large body of research has been published on neuroimaging-based computer-aided classification of AD and its prodromal stage, mild cognitive impairment (MCI). Motivated by this rapid proliferation of AD/MCI classification studies and the lack of literature summarizing different AD-related features as extracted from neuroimaging data and classification algorithms, we present an overview of pertinent advances in this field. We summarize key representative studies on neuroimaging-based classification of AD/MCI and provide a brief account of the main aspects of these studies, such as study population, type of features, the adopted classification algorithm, and the reported classification success rates. Furthermore, we highlight several bottlenecks (i.e. limited sample size and variability in data settings across the different studies) and discuss the generalizability and reproducibility of existing AD classification studies, as well as the important and largely unexplored issue of heterogeneity in AD.

Recent review papers (Arbabshirani et al., 2017; Falahati et al., 2014) reported studies on MRI- and multimodality-based classification of AD and MCI, limiting AD classification to MRI or its combination with other modalities only. Pathological brain changes related to AD can be captured via various other independent imaging modalities, such as FDG-PET and amyloid-PET, therefore, a comprehensive review on AD classification should also include studies using FDG-PET and amyloid-PET only. This review is further unique in that it focuses exclusively on those studies that have extensively leveraged cross-validation strategies to estimate the performance of their classification frameworks. Cross-validation is generally designed to achieve independent training and test data for a classification algorithm and defined as split the data once (split-in-train-test) or several times (k-fold cross-validation) to obtain an unbiased estimate of the classification performance of the algorithm and avoid over fitting (Arlot and Celisse, 2010; Kohavi, 1995). In the split-in-train-test, data is randomly divided into independent training and test subsets, optimally with matched demographic characteristics. The training subset is used solely for the learning procedure of the classification algorithm and the test subset is used to estimate the performance of the trained classification algorithm. In k-fold, data is divided into k-folds and a classification algorithm is tested on kth fold after being trained on k-1 folds in kth iteration. Furthermore, we provide in-depth detail about AD-related feature extraction methods from various neuroimaging modalities, important information that is mostly lacking in existing review papers.

Selection criteria

We searched in PubMed and Google Scholar, from January 1985 to June 2016, and identified 409 studies based on the given search criteria. We included original peer-reviewed research studies that exclusively used cross-validation strategies to estimate the performance of their classification frameworks. In addition, studies conducted for method comparisons and studies not focusing primarily on AD classification were excluded from this review. Finally, this criterion resulted in 81 studies that were reviewed and presented here. A more thorough explanation of the search and screening process with flow chart figure, and databases generated from the search in Google Scholar and PubMed are provided in the Supplementary Material.

Classification frameworks for Alzheimer's disease and its prodromal stages

Over the past decade, classification frameworks have been used successfully to analyze complex patterns in neuroimaging data with a view to the classification of AD and MCI subjects. A classification framework is comprised of four major components: feature extraction, feature selection, dimensionality reduction, and feature-based classification algorithm. Feature extraction and classification algorithm are