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Predicting conversion from MCI to AD by integrating rs-fMRI and structural MRI

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ABSTRACT

Structural MRI (sMRI) and resting-state functional MRI (rs-fMRI) have provided promising results in the diagnosis of Alzheimer's disease (AD), though the utility of integrating sMRI with rs-fMRI has not been explored thoroughly. We investigated the performances of rs-fMRI and sMRI in single modality and multi-modality approaches for classifying patients with mild cognitive impairment (MCI) who progress to probable AD-MCI converter (MCI-C) from those with MCI who do not progress to probable AD-MCI non-converter (MCI-NC). The cortical and subcortical measurements, e.g. cortical thickness, extracted from sMRI and graph measures extracted from rs-fMRI functional connectivity were used as features in our algorithm. We trained and tested a support vector machine to classify MCI-C from MCI-NC using rs-fMRI and sMRI features. Our algorithm for classifying MCI-C and MCI-NC utilized a small number of optimal features and achieved accuracies of 89% for sMRI, 93% for rs-fMRI, and 97% for the combination of sMRI with rs-fMRI. To our knowledge, this is the first study that investigated integration of rs-fMRI and sMRI for identification of the early stage of AD. Our findings shed light on integration of sMRI with rs-fMRI for identification of the early stages of AD.

1. Introduction

Alzheimer's disease (AD), a progressive, irreversible neurodegenerative disorder, occurs most frequently in older adults and gradually destroys regions of the brain that are responsible for memory, thinking, learning, and behavior. The diagnoses of AD and its prodromal stage referred to as mild cognitive impairment (MCI) have attracted much attention in recent decades. MCI refers to a clinical syndrome characterized by significant cognitive impairments, which are beyond normal for healthy adults, but not sufficient to meet clinical criteria for AD. The rate of conversion from MCI to overt dementia is substantial, at 15% per year [1]. The amnestic subtype of MCI has a high risk of progression to AD, constituting a prodromal stage of AD [2].

Biomarkers based on positron emission tomography (PET), structural magnetic resonance imaging (sMRI), and resting-state functional MRI (rs-fMRI) have provided promising results for discriminating MCI from AD [3–5]. MRI-based biomarkers have been used to identify the early stage of AD [6–8]. In a recent study, six anatomical MRI measures, e.g. cortical surface area and subcortical volumes, were used to discriminate AD patients from controls, and an area under the receiver operating characteristic (ROC) curve (AUC) of 0.98 was reported [9]. Eskildsen et al. [6] used patterns of cortical thickness and identified cortical regions potentially discriminative for separating MCI converter (MCI-C) patients from MCI patients who remained stable for three years (MCI-NC). They reported a maximum accuracy of 76% for classifying MCI-C from MCI-NC.

The rs-fMRI connectivity analysis can assist in the diagnosis of diseases associated with alteration of the brain network, even before

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brain atrophy has emerged. Since cognitive and behavioral functions rely on large-scale network interactions, the rs-fMRI connectivity analysis may clarify fundamental aspects of disease pathophysiology [10]. The rs-fMRI connectivity analysis has been utilized to detect alteration of the brain networks in MCI and AD [11–15]. A previous study reported that some brain networks were selectively disrupted in AD, while other networks might be affected by AD pathology at the early stage of AD [16]. While previous studies demonstrated the ability of rs-fMRI in the identification of patients with AD from healthy controls or patients with MCI [17–21], the utility of rs-fMRI in the prediction of the early stage of AD, also the classification of MCI-C from MCI-NC, has not been completely explored [22].

AD has been associated with several imaging biomarkers, including brain atrophy measured through sMRI, particularly in the hippocampus and posterior cingulate gyrus [23,24], hypometabolism in the temporal and parietal lobes measured via FDG-PET [25,26], and abnormal fractional anisotropy (FA) and mean diffusivity (MD) in hippocampus and other structures [27–29]. It is expected that the biomarkers based on these neuroimaging modalities have complementary information, and thus a multi-modal approach may improve our understanding of AD over that presented by one modality [28]. Previous neuroimaging studies in the diagnosis of AD have mainly focused on single modality approaches, although some evidence has demonstrated that a multi-modal imaging approach can improve accuracy of this diagnosis [5]. Previous multi-modal studies in AD diagnosis have integrated MRI, diffusion tensor imaging (DTI), PET, cerebral blood flow (CBF), and/or electroencephalography (EEG) [30,31]. Arbabshirani et al. [32] performed a comprehensive review of neuroimaging-based single subject prediction for MCI, AD, and other neurological and psychiatric diseases. They concluded that: 1) there is widespread evidence demonstrating the potential of neuroimaging data for prediction of AD and other diseases; and 2) most studies reported superior performance of a multi-modal approach compared to single modality. Hinrichs et al. [33] reported that clinical and imaging data (MRI and fludeoxyglucose (FDG)-PET) can be successfully combined to predict AD using machine-learning techniques. They found that the imaging modalities had a better performance in prediction of AD compared to clinical data [33]. The complementary aspects of EEG and sMRI data in the modeling of language ability and other cognitive functions in pathologic aging have been demonstrated [34,35]. It was reported that patients with MCI can be identified using a combination of the amplitude of the resting-state EEG in alpha band and the hippocampal atrophy, extracted from sMRI [36,37].

Previous studies integrated rs-fMRI with other imaging modalities in AD diagnosis, although the results of these studies are not consistent [38,39]. Some of these studies reported that integrating rs-fMRI with other modalities improved the performance of classifying AD from controls [39,40]. It was also reported that this integration did not improve performance of the classification [38]. Schouten et al. [39] investigated the performances of uni-modal and multi-modal approaches for classification of patients with MCI and AD using an elastic net classifier based on several measures derived from sMRI, DTI, and rs-fMRI. They reported that the AUC of unimodal classification ranged from 0.76 for rs-fMRI to 0.91 for sMRI. They obtained an AUC of 0.95 for the classification of patients with MCI and AD by combining sMRI, DWI, and rs-fMRI measures. They concluded that combining multiple MRI modalities can considerably improve classification performance over uni-modal classification. Dyrba et al. [38] investigated a multi-modal approach based on sMRI, DTI, and rs-fMRI to classify AD from HC using support vector machine (SVM). They obtain an AUC of 86% for sMRI, 87% for DTI, and 80% for rs-fMRI to classify AD from HC using a single modality approach. For multi-modal approaches, they obtained an AUC of 82% using all three modalities and 89% using a combination of DTI with sMRI. They concluded that combining rs-fMRI with other MRI modalities may not significantly improve classification accuracy compared to SMRI or DTI alone.

In addition to the discrepancy in the literature about whether or not integration of rs-fMRI with other imaging modalities can improve accuracy of AD classification, there is no study to evaluate the performance of integrating rs-fMRI with other modalities, e.g., sMRI, in prediction of the early stage of AD and classifying MCI-C from MCI-NC. To address these deficiencies, we evaluated the performances of rs-fMRI and sMRI in single modality and multi-modality approaches to predict the early stage of AD. To achieve the best performance in this prediction, we investigated the application of two atlases for parcellation of the brain regions for each modality. After extraction of graph measures from rs-fMRI and structural measures, e.g., cortical thickness, from sMRI, we used these measures as input features of our feature selection algorithm to identify a small subset of optimal features. Selection of appropriate features not only removes the non-informative inputs, but it also reduces the computational time involved in classification [41]. We utilized these optimal features in a machine learning approach based on the SVM to accurately classify MCI-C from MCI-NC.

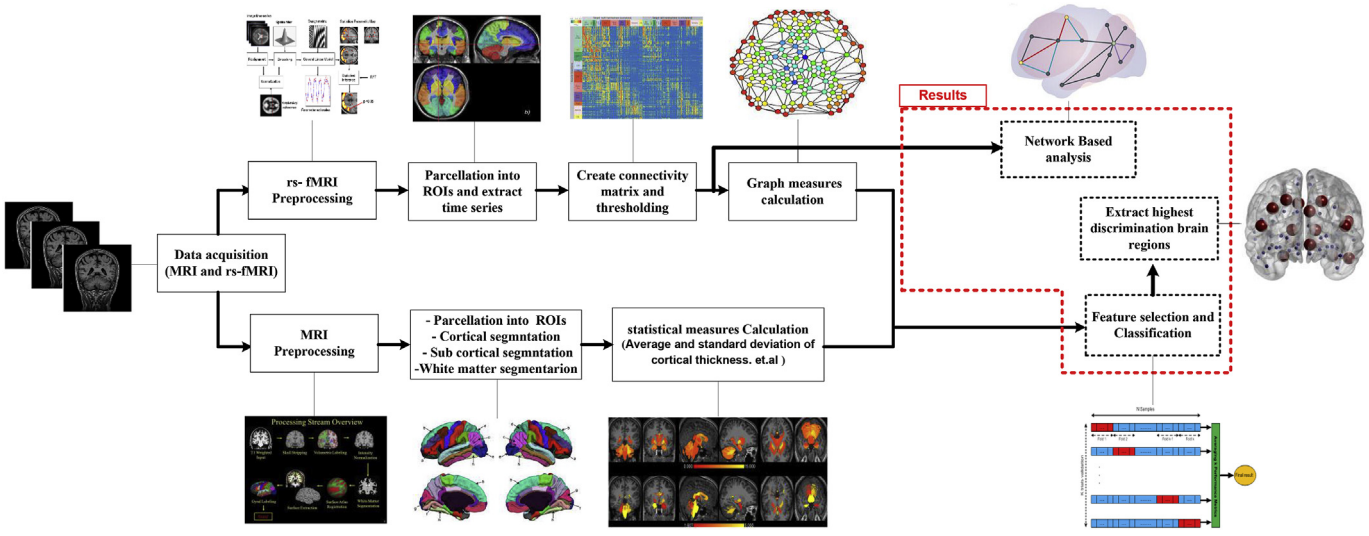

Fig. 1. The overall procedure for this study.