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Early prediction of the Alzheimer's disease risk using Tau-PET and machine learning

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ABSTRACT

Alzheimer's Disease (AD) is a devastating neurodegenerative disease. Recent advances in tau-positron emission tomography (PET) imaging allow quantitating and mapping out the regional distribution of one important hallmark of AD across the brain. There is a need to develop machine learning (ML) algorithms to interrogate the utility of this new imaging modality. While there are some recent studies showing promise of using ML to differentiate AD patients from normal controls (NC) based on tau-PET images, there is limited work to investigate if tau-PET, with the help of ML, can facilitate predicting the risk of converting to AD while an individual is still at the early Mild Cognitive Impairment (MCI) stage. We developed an early AD risk predictor for subjects with MCI based on tau-PET using Machine Learning (ML). Our ML algorithms achieved good accuracy in predicting the risk of conversion to AD for a given MCI subject. Important features contributing to the prediction are consistent with literature reports of tau susceptible regions. This work demonstrated the feasibility of developing an early AD risk predictor for subjects with MCI based on tau-PET and ML.

Keywords: Alzheimer's disease, mild cognitive impairment, tau-PET, machine learning, early detection, risk prediction

1. INTRODUCTION

Alzheimer's Disease (AD) is a devastating neurodegenerative disease[1]. Early detection is critically important, as it allows timely intervention that holds the promise of slowing down disease progression. Mild Cognitive Impairment (MCI) is an early phase when patients show symptoms of memory loss and cognitive decline, but the symptoms are not too severe to disrupt their ability to perform daily activities. However, MCI has substantial heterogeneity as it can be caused by various underlying brain disorders including AD.

Two well-known neuropathological hallmarks of AD are neuritic plaques composed of β-amyloid fibrils and neurofibrillary tangles composed of hyperphosphorylated tau[2]. In vivo imaging of these hallmarks across the brain provides an important tool for detection and mechanistic understanding of the disease. Past research has focused on amyloid-PET imaging that provides an in vivo measure of the Aβ burden[3]. With the recent advances in tau-PET imaging[4-5], there is an urgent need to develop Machine Learning (ML) algorithms to interrogate the utility of this new imaging modality. While there are some recent studies[6] showing promise of using ML to differentiate AD patients from normal controls (NC) based on tau-PET images, there is limited work to investigate if tau-PET, with the help of ML, can facilitate predicting the risk of converting to AD while an individual is still at the early MCI stage.

The purpose of this work is to develop a tau-PET-based AD risk predictor for subjects with MCI using ML. Specifically, we trained multiple ML classifiers to classify AD and NC based on tau-PET. The trained classifiers were then used to predict the risk of conversion to AD for each MCI subject. The classifiers show good accuracy, sensitivity and specificity to predict MCI conversion to AD. Also, important features contributing to the prediction are consistent with literature reports of tau susceptible regions. This work demonstrated the feasibility of developing an early AD risk predictor for subjects with MCI based on tau-PET and ML.

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2. DATA

2.1 Patient inclusion

We used data from the Alzheimer's Disease Neuroimaging Initiative[7] (ADNI) databases. Tau-PET images were collected relatively recently by ADNI (ADNI 3). This study included 67 AD, 393 NC, and 144 MCI subjects with tau-PET images. For each MCI subject at baseline (defined as the time point when the subject has an MCI diagnosis and also has tau-PET available), if the subject was diagnosed as AD in a follow-up visit within 24 months, the person was called a converter. Otherwise, the person was called a non-converter. According to this definition, there are 31 converters and 113 non-converters in this dataset.

2.2 Image processing and feature extraction

We used a regional standardized update value ratio (SUVR) of tau-PET images extracted by the ADNI PET core, among which 84 cortical and sub-cortical SUVR features were included in ML training. All features were normalized using the inferior cerebellum as the reference region.

2.3 Other clinical features

In addition to imaging features, standard demographic and cognitive features such as gender, age, MMSE scores were also included.

3. METHODOLOGY

3.1 Training of machine learning classifiers

We trained an AD risk predictor based on tau-PET features of AD and NC subjects. Four ML classifiers were studied so that the results can be cross-referenced to account for model uncertainty. These classifiers include Random Forest (RF), Gaussian Process (GP), Support Vector Machine (SVM) and logistic-lasso. 10-fold cross-validation was used to evaluate the model performance.

3.2 Prediction of conversion-to-AD risk for MCI subjects

The trained classifiers were used to generate a predicted probability of AD for each MCI subject. This probability represents the risk of an MCI subject converting to AD in 24 months. We computed several metrics to evaluate the prediction accuracy:

(1). Binary classification: If the probability is greater than 0.5, the MCI subject is classified as having a high risk of AD, namely class 1; otherwise, the subject is classified as class 2. Then, we constructed a confusion matrix of the predicted classes versus the true classes of conversion or non-conversion by 24 months. We reported accuracy, sensitivity, and specificity computed based on the confusion matrix.

(2). Rank correlation: To consider the different conversion months among converters and account for censored data in non-converters, we computed a rank correlation between the predicted probabilities and the conversion times of all MCI patients, (12, 24, 12, 36, … 12+, 24+, … months), where a number without "+" corresponds to the conversion month of a converter and a number with "+" corresponds to the last follow-up month of a non-converter.

3.3 Consistency of risk prediction across ML algorithm

We computed the agreement of risk prediction by different ML algorithms using intra-class correlation (ICC), which is the correlation between the predicted probabilities from different classifiers on the same subject.

3.4 Image feature contribution to risk prediction

We computed the SHAP[8] (SHapley Additive exPlanations) value of each tau-PET feature used to build the classifier. SHAP is a popular, model-agnostic approach to quantify feature contributions. The higher the absolute SHAP value of a feature, the greater impact the feature on the classification. The sign of the SHAP value indicates if the feature has a positive or negative impact on the probability of a sample belonging to one class against the other class.

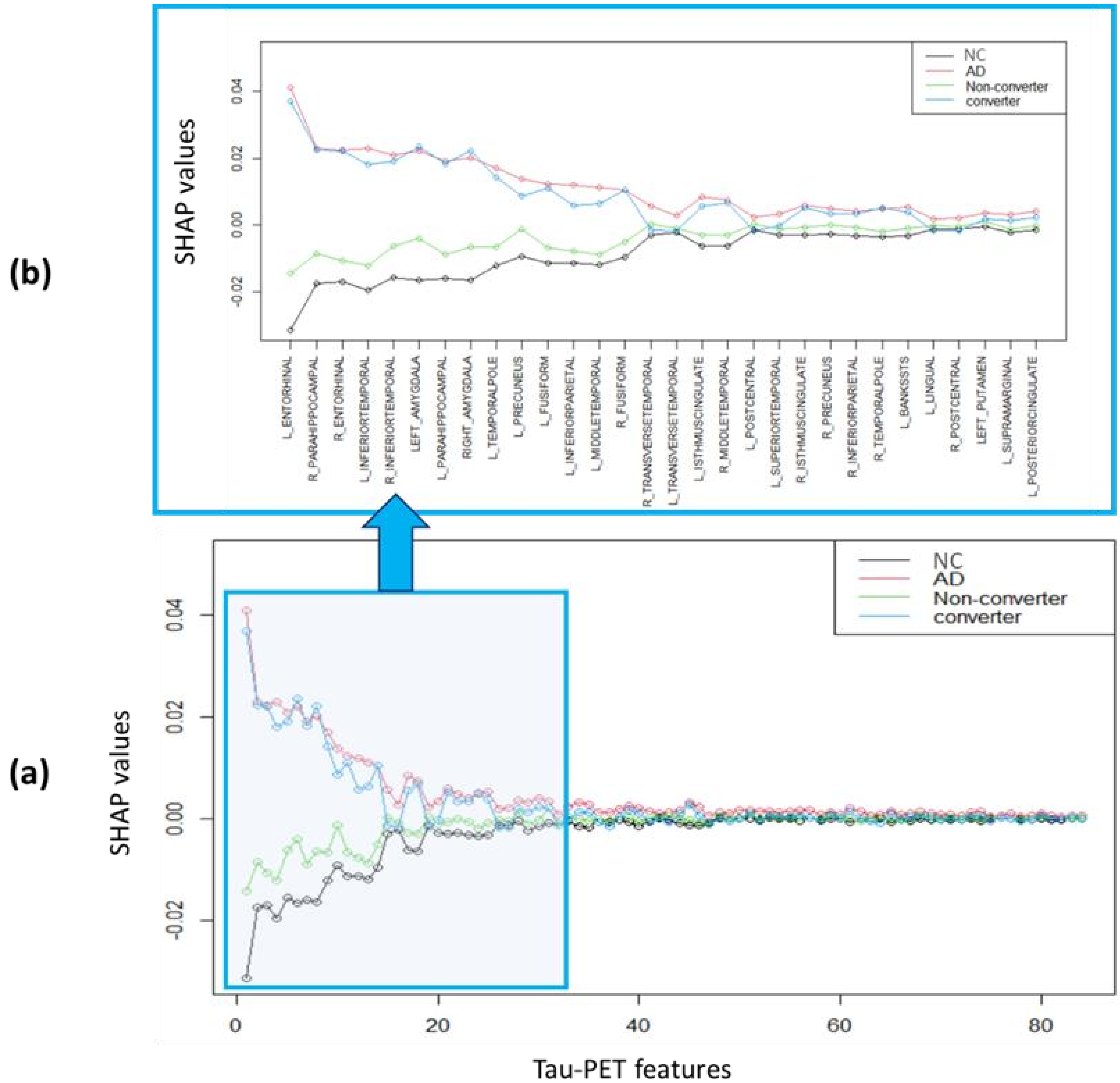

Figure 1. SHAP values of tau-PET features: (a) all 84 features; (b) zoom-in of the first 30 features with names.

4. RESULTS

4.1 Accuracy of AD vs NC classification

Based on 10-fold cross-validation, the AD vs. NC classification using four ML classifiers achieves on average 0.89 accuracy, 0.80 sensitivity, and 0.91 specificity. Also, the agreement of the classification results by the different algorithms is high, with an average ICC of 0.83. When including demographic/clinical features of gender, age, and MMSE, the performance improved to 0.95 accuracy, 0.91 sensitivity, and 0.95 specificity.

4.2 Prediction of conversion-to-AD risk for MCI subjects

The trained AD vs. NC classifiers were used to generate a probabilistic AD risk score for each MCI subject. Using the 0.5 probability cutoff and 24-month conversion time frame, the trained classifiers achieved on average 0.77 accuracy, 0.82

sensitivity, and 0.75 specificity in predicting MCI conversion. Furthermore, the rank correlation between the predicted probabilities and the conversion times of all MCI subjects is -0.69, meaning a moderately high negative correlation between the AD risk and the time to conversion. Additionally, the agreement of the classification results on each MCI subject by the different algorithms is high with an average ICC of 0.85.

Using the trained classifiers that included both imaging and demographic/clinical features, the performance in risk prediction of MCI subjects became 0.79 accuracy, 0.78 sensitivity, and 0.79 specificity, which did not show a significant difference from the result of using imaging features only.

4.3 Image feature contribution to risk prediction

Fig. 1(a) shows the group-averaged SHAP values of 84 regional SUVR features, where the four groups are AD, NC, converters, and non-converters. The features are ordered according to the absolute SHAP value of each feature averaged over all subjects in the training model (i.e., the AD vs. NC classifier), which represents the contribution of each feature to the classifier. Fig. 1(b) zooms in to the first 30 features with feature names spelt out. Regions of the most contributing features such as entorhinal, parahippocampal, inferior-temporal, amygdala, and others are consistent with findings in the literature.

Furthermore, there is a clear separation between AD and NC with positive/negative SHAP for AD/NC, especially for the first 10-20 features. A positive SHAP value of a feature means that a higher SUVR in the corresponding region is associated with a higher risk of AD, and vice versa. The trends in Fig. 1 make sense. Interestingly, SHAP of the converter group is on the same (positive) side as AD, while SHAP of the non-converter group is on the same (negative) side of NC. This explains the high accuracy of using the trained AD vs. NC classifier to predict the AD conversion risk of MCI subjects. Note that in Fig. 1 we only included the result from the RF classifier as the SHAP of FR can be efficiently computed.

5. CONCLUSION

This work interrogated the utility of tau-PET imaging, with the help of ML, for predicting the risk of conversion to AD while the individual is still at the early MCI stage. We trained multiple ML classifiers to differentiate AD vs. NC based on regional SUVR features extracted from tau-PET images. The trained classifiers achieved high accuracy in predicting the risk of conversion to AD for MCI subjects. We investigated and ranked the contributions of different features in the ML classifier/predictor and found that regions corresponding to important features are consistent with literature reports of tau susceptible regions based on prior clinical/pathological knowledge.

6. DECLAIMER

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