

Explainable Machine Learning Reveals MRI Signatures Of Alpha-synuclein Co-pathology In Alzheimer's Disease

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BACKGROUND

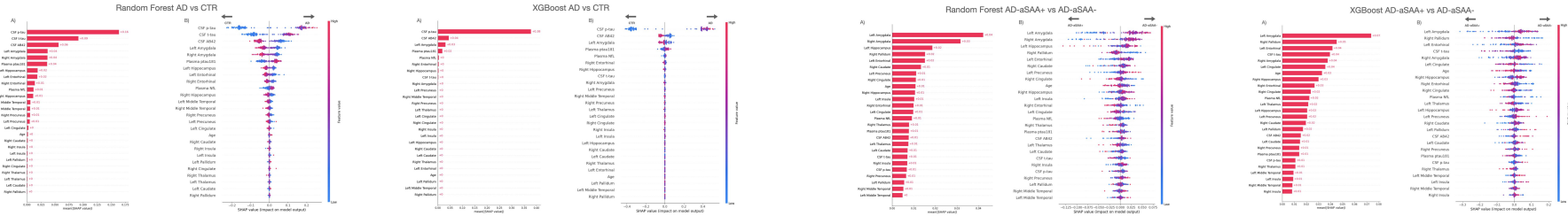
Alpha-synuclein (α -syn) copathology is frequently observed in patients with Alzheimer's disease (AD) and is associated with faster disease progression and poorer treatment response. In vivo detection of α -syn pathology using the alpha-synuclein seed amplification assay (α -syn SAA) shows high sensitivity; however, its clinical implementation remains limited due to restricted availability. MRI is a widely available technique that can identify brain atrophy patterns associated with specific pathologies. However, it may not capture the subtle structural differences associated with α -syn co-pathology using conventional analyses. In this context, explainable artificial intelligence (XAI) applied to multimodal data may provide an accessible alternative to identify biological and structural signatures associated with α -syn copathology using structural magnetic resonance imaging (MRI), a widely available clinical tool.

METHODS

A total of 226 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort were included: 142 individuals with AD and an A+T+ biomarker profile, and 84 cognitively normal healthy controls (CTR, A-T- α -syn-). AD patients were stratified according to α -syn SAA results into AD α -syn+ (n=44) and AD α -syn- (n=98). Multimodal data were analysed, including cerebrospinal fluid (CSF) biomarkers, plasma biomarkers, and regional brain volumes derived from structural MRI. Explainable machine learning models (Random Forest and XGBoost) were trained to perform two classification tasks: AD vs. CTR and AD α -syn+ vs. AD α -syn-. Model interpretability was assessed using Shapley Additive exPlanations (SHAP) to identify the relative contribution of each variable to the classification outcomes.

RESULTS

Fig.: A) Mean absolute SHAP values are shown in descending order, representing each feature's overall contribution to the classification task. B) SHAP summary plot: each point corresponds to one individual's SHAP value for a given feature. Color indicates the feature value (red = high, blue = low). When a data point is located on the left (right) of the y-axis, it represents an instance with a negative (positive) SHAP value for the specific feature, reflecting this feature's contribution to the instance being classified in the AD- α SAA+ (AD- α SAA-) group. Features are ranked based on their importance values in absolute value.



Both Random Forest and XGBoost showed excellent performance in distinguishing AD dementia from controls, achieving accuracies of 99.4 $\pm$ 1.3% and 98.2 $\pm$ 2.4%, respectively, with an AUC of 1.0 for both models. SHAP analysis identified CSF p-tau181 as the strongest predictor in both algorithms, followed by established AD biomarkers including low CSF A β 42, elevated plasma p-tau181 and NFL, and MRI-based atrophy in regions such as the hippocampus, entorhinal cortex, and middle temporal gyrus. Overall, both models reliably captured known CSF, plasma, and MRI signatures of AD, supporting their use as robust classifiers and as tools to explore α -syn+ AD-specific patterns.

Random Forest and XGBoost showed meaningful though moderate performance in distinguishing AD individuals with and without α -syn copathology, with Random Forest achieving 70.5 $\pm$ 3.1% accuracy and XGBoost reaching 64.1 $\pm$ 1.8%. SHAP analysis revealed biologically interpretable signatures associated with α -syn copathology, highlighting structural MRI features as key contributors—especially amygdala, pallidum, hippocampus, entorhinal cortex, cingulate, caudate, insula, and precuneus. AD- α SAA+ individuals were characterized by greater limbic and cortical atrophy and lower CSF A β 42, whereas AD- α SAA- individuals showed associations with older age, higher selected regional volumes, and increased plasma and CSF neurodegeneration/tau biomarkers.

CONCLUSIONS

XAI applied to multimodal biomarkers enables the identification of disease-specific structural and biological signatures associated with α -syn copathology in Alzheimer's disease. This approach represents a promising tool for in vivo phenotyping, patient stratification, and the development of more personalized therapeutic strategies, particularly in clinical settings where α -syn SAA is not readily available.

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