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GENETICS

Interpretable deep learning framework towards understanding molecular changes associated with neuropathology in human brains with Alzheimer's disease

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Abstract

Background: Postmortem brain tissues have been used to characterize some of the molecular networks and drivers associated with Alzheimer's disease (AD). In this study, we extend our previous work of a deep learning approach to characterize the molecular changes associated with the severity of AD-related neuropathology and cognitive impairment, by applying the framework to different brain regions with larger sample sizes.

Method: We trained multi-layer perceptron (MLP) models for classification of neuropathologically confirmed AD vs. healthy controls (HC) using the transcriptomic data of three brain regions (dorsolateral prefrontal cortex (DLPFC, Total N = 1092), posterior cingulate cortex (PCC, Total N = 647), and head of caudate nucleus (HCN, Total N = 717)) respectively from the ROSMAP study. We performed z-score normalization for each gene expression and randomly split data in ratio 80:20 with matching class (AD and HC) distributions for training and testing. We embedded the expression profiles of all the subjects to the same Uniform Manifold Approximation and Projection (UMAP) space using the final layer of the trained models and obtained progressive trajectories that mirrored AD pathological severity and cognitive impairment of the whole cohort. Interpretable technique SHapley Additive exPlanations (SHAP) was explored to explain model predictions and obtain significant genes contributing to AD. Network analysis was then carried out to identify key gene modules presented in the models underlying AD progression of different brain regions.

Result: The MLP models differed for each dataset with the number of layers ranging between 3-5 and achieved the best AUC of 0.891, 0.940 and 0.776 on DLPFC, PCC and HCN datasets respectively. The AD severity indexes (SI) calculated from the trajectory were highly correlated with neuropathology biomarkers ($R \sim 0.6$, $p < 1e\text{-}11$) and global cognitive function ($R \sim 0.7$, $p < 2.2e\text{-}16$). Significant genes identified by the SHAP explainer revealed common and specific transcriptomic signatures from different brain regions implicated in AD.

Conclusion: This study illustrates the potentials of deep learning methods to multi-omic data to characterize the molecular networks associated with increasingly severe clinical and neuropathological stages of neurodegenerative diseases like AD. This offers the opportunity to discover drug targets and/or biomarkers.