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Detection of Tau pathology in Alzheimer's disease brain tissues using deep learning

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects memory, cognition, and behavior. Aberrant accumulation of intracellular forms of hyperphosphorylated Tau protein (pTau) has been identified as a key biomarker for AD. However, these forms have small and subtle morphology and can often only be discerned at high magnifications. Consequently, manual assessment by an expert pathologist is time-consuming and subject to inter-observer variability. Deep learning methods have proven effective in the unbiased detection of pathology in various tissues, including brain tissue.

Objective: This study aims to apply and validate a convolutional neural network (CNN) as part of an intuitive, automated workflow for accurately detecting pTau pathology in pTau-targeted whole-slide immunohistochemistry (IHC) images of human brain tissues. The proposed model will output a probabilistic map showing pTau positivity of user-defined regions of interest (ROIs) and anatomically defined areas. Our goal is to enhance the efficiency, reproducibility, and objectivity of pTau pathology assessments, thus leading to faster and more efficient diagnoses.

Methods: FFPE brain tissue blocks from 7 subjects diagnosed with AD were immunohistochemically (IHC) targeted by pTau antibody, and the resulting whole slide images (WSIs) were imaged at 40X resolution. A clinical pathologist reviewed the IHC images and annotated ROIs that were representative of positive or negative regions. Over 3 million 224x224 pixel patches were generated from the ROIs, which were used as inputs to train a VGG19 CNN model with a train-validation-test split of 70-15-15. Patch-level predictions were aggregated within each ROI and across each anatomical region to compare the model's ability to evaluate the probability of pTau positivity across various regions of the brain.

Results: The model was trained for 6 epochs before training was halted due to a lack of improvement. On a test set of patches randomly selected from all the ROIs, our model achieved precision = 0.75, recall = 0.35, and F1 score = 0.47, indicating a high proportion of false negative predictions. When patches were aggregated among each ROI using top k features (k=50) the model achieved precision = 0.37, recall = 0.76, and F1 score = 0.51. This shows a considerable drop in the false negative rate, which is desirable for detecting pathology.

Conclusion: We demonstrated that our workflow could process annotated WSIs into suitable training data, feed them into a widely used CNN model for IHC images, and evaluate the model's performance using a test set. While the final model performed unreliably at the patch level, it performed better when aggregated by ROI. Learning was hindered by significant variations in WSI backgrounds across subjects. Future efforts should consider histogram normalization before training to mitigate the effect of technical variation, and train for more epochs to maximize the model's ability to learn structural features.