Neuro-Tau Visions: Ablation Study and Biomarker Correlations in Alzheimer's Disease

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***Abstract*—Neurodegenerative diseases represent a significant and escalating global challenge, particularly as populations age. Alzheimer's disease (AD), the most prevalent form of dementia, currently affects over 45 million people worldwide, with projections indicating a potential tripling of this number by 2050. This alarming escalation underscores the urgent need for early diagnostic methods capable of detecting AD before the emergence of clinical symptoms. Biomarkers are invaluable in this context, offering a promising pathway for predicting the early onset of Alzheimer's disease. The role of biomarkers in the early detection of Alzheimer's is critically important. They facilitate the identification of pathophysiological changes well before the initial symptoms of cognitive decline become evident. Research indicates that these changes may occur one to two decades prior to the noticeable onset of cognitive impairment. This substantial "window of opportunity" for early intervention is pivotal, as it provides a possibility for treatments that might slow or even halt the progression of the disease before significant brain damage ensues. Early detection is crucial not only for enhancing the quality of life for patients but also for lessening the burden on caregivers and healthcare systems. By diagnosing Alzheimer's disease in its early stages, it becomes possible to manage its progression more effectively through customized interventions. This method is in line with the shift towards personalized medicine in the management of chronic conditions, including neurodegenerative disorders. Our study demonstrates the potential of multilayer perceptrons in predicting tau protein accumulation in the brain. Using a comprehensive grid search and nested cross-validation approach, we ensured robust predictive performance across different outer folds. An ablation study and feature importance analysis highlighted the critical role of demographic and regional connectivity features in accurate prediction. However, outliers identified in Figures 4 to 8 suggest the need for improved noise assessment. Future work will focus on refining our approach to handle such outliers effectively.**

***Index Terms*—Early Alzheimer's Detection, Biomarker Research, Neurodegenerative Diseases, Predictive Models, Tau Protein Accumulation, Ablation Study, Personalized Medicine, Cognitive Decline, Pathophysiological Biomarkers, Early Intervention.**

I. Introduction

THE Accumulation of tau protein in the brain is a hallmark of neurodegenerative diseases like Alzheimer's disease (AD), contributing significantly to the onset and progression of cognitive decline. Several factors, including genetic mutations, biochemical alterations, environmental influences, and aging, impact tau accumulation and its distribution across brain regions. For instance, mutations in the MAPT gene or the presence of the APOE4 allele predispose individuals to tauopathies by impairing tau's ability to stabilize microtubules or accelerating its pathological aggregation. Additionally, environmental factors and lifestyle choices can exacerbate biochemical processes leading to tau accumulation, particularly in older individuals. Understanding these risk factors and their interactions is crucial for developing effective predictive models and targeted interventions.

Development of reliable biomarkers for early detection stands as a fundamental aspect of contemporary Alzheimer's research. Prioritizing this area promises improved outcomes for patients and is a critical step towards addressing the expected surge in dementia cases. As the prevalence of Alzheimer's disease increases, the urgency for such advancements becomes more pronounced. Early intervention capabilities could dramatically alter the course of the disease, transforming Alzheimer's from an inevitable deterioration into a manageable condition.

Advancements in machine learning have enabled the development of predictive models that can identify patterns in complex biomedical data. Multilayer perceptrons (MLPs), a type of artificial neural network, are particularly well-suited for predicting tau protein accumulation due to their ability to learn non-linear relationships. In this study, we utilized a comprehensive grid search and nested cross-validation approach to assess the predictive performance of MLPs in forecasting tau protein accumulation across 80 brain regions. Our models used a diverse set of input features, including demographic, genetic, biochemical, and imaging data, to generate accurate predictions. An ablation study and feature importance analysis further highlighted the significance of demographic and regional connectivity features in improving model accuracy.

The outline of the contributions of this report can be summarized as:

- Ablation study to compare the capabilities of different models in predicting Tau values. Models include variations such as:
  - **Model 1**: Tau, Amyloid-beta levels (Amy), and t.
  - **Model 2**: Tau, Amyloid-beta levels (Amy), demographics, patient health data, and t.
  - **Model 3**: Tau and t only.

Section II provides a background on factors influencing tau accumulation, such as genetic, biochemical, environmental, and age-related factors, and underscores the importance of early diagnosis.

Section III reviews key literature on Alzheimer's disease pathology and modeling approaches, including reaction-diffusion models, partial differential equations, protein propagation dynamics, and prion-like features.

Section IV explains data acquisition and handling, detailing

the creation of a unified dataset and our data stratification methods. Section V presents the results of multilayer perceptron models predicting tau accumulation values across 80 brain regions, while the ablation study compares different feature sets, and predictive performance is visualized across age, sex, and APOE4 gene groups.

Section VI discusses the implications of the results, highlighting the significance of demographic and regional connectivity features in predicting tau accumulation and identifying challenges in predicting tau accumulation in younger individuals and those with two copies of the APOE4 gene.

Section VII summarizes the key findings, emphasizing the promising predictive performance of multilayer perceptrons and the need to refine models to address noise and discrepancies.

Section VIII outlines future research plans to refine methodology by improving noise assessment, addressing outliers, and enhancing predictive models to handle variability in tau accumulation due to genetic and demographic factors.

II. Factors Affecting Tau accumulation

Tau protein accumulation in brain regions is a crucial pathological feature of several neurodegenerative diseases, including Alzheimer's disease. Multiple factors influence Tau accumulation, affecting both its rate and distribution within the brain.

Genetic Factors: Certain genetic mutations, particularly in the *MAPT* gene which encodes Tau, lead directly to tauopathies by altering the protein's ability to stabilize microtubules [3]. Additionally, the presence of the APOE4 allele is another significant genetic factor influencing Tau pathology. Individuals carrying one copy of the APOE4 allele (heterozygous) are at increased risk of developing Alzheimer's, while those with two copies (homozygous) have an even higher risk and typically experience an earlier onset and faster progression of the disease [4].

Biochemical Factors: Post-translational modifications of Tau, such as hyperphosphorylation, acetylation, and truncation, disrupt its normal function, contributing to neurofibrillary tangle formation, a hallmark of Tau pathology [5].

Environmental Factors: Lifestyle choices, environmental toxins, and even repeated head trauma are implicated in exacerbating biochemical processes leading to Tau accumulation [6].

Age: Aging is one of the most significant risk factors, as older brains are more susceptible to processes that trigger Tau dysfunction and aggregation [7].

Neuroinflammation: Chronic brain inflammation significantly affects Tau pathology by enhancing phosphorylation or impairing clearance, promoting Tau aggregation [8].

Understanding these factors is essential for developing targeted interventions to mitigate Tau accumulation before it leads to neurodegeneration. Potential strategies include genetic therapy, lifestyle modifications, or pharmacological interventions to modulate Tau's post-translational modifications or enhance its clearance.

A. The Importance of Effective Early Diagnosis

Effective early diagnosis is one of the critical components of addressing neurodegenerative diseases. It serves as a cornerstone in the management and treatment of conditions like Alzheimer's and Parkinson's disease. By identifying these diseases in their early stages, healthcare professionals can intervene promptly, potentially slowing down their progression and improving patient outcomes.

One of the critical components of effective early diagnosis is the ability to recognize subtle signs and symptoms that may indicate the onset of a neurodegenerative condition. This requires a combination of clinical expertise, advanced diagnostic tools, and an understanding of the underlying mechanisms of these diseases.

In summary, effective early diagnosis holds immense significance in the realm of neurodegenerative diseases. Therefore, it is crucial to consider its implications across various fields:

- Scientifically: Early diagnosis informs the design of therapeutic trials by identifying optimal time points for intervention and data collection. It allows researchers to understand the disease progression better and evaluate the efficacy of potential treatments[9].
- Economically: Early diagnosis provides insights into estimating the socioeconomic impact of neurodegenerative diseases more accurately. By understanding the prevalence and progression of these conditions, policymakers can allocate resources more effectively and develop targeted interventions[10].
- Clinically: Timely diagnosis helps pinpoint the most effective periods for pharmacological interventions. It allows healthcare providers to tailor treatment plans to individual patients, potentially altering the course of the disease and improving long-term outcomes. Additionally, early diagnosis enables early initiation of supportive therapies and lifestyle interventions, further enhancing patient care[11].

III. Literature Review

In our literature review focused on Alzheimer's disease, we have explored a series of key papers that provide insights into the underlying mechanisms and modeling approaches associated with Alzheimer disease pathology.

The first paper we examined, "Reaction-Diffusion Model as a Framework for Understanding Biological Pattern Formation," [12] outlines Turing's Reaction-Diffusion (RD) model. This model elucidates how self-organized patterns, such as those observed in neurological structures, can emerge from interactions between diffusible substances. A significant aspect of the RD model is its introduction of morphogens, which are instrumental in tissue development and cellular positioning. This concept extends to the neurological context, suggesting a potential for using RD models to predict Tau protein distribution along axons, an element crucial in the study of Alzheimer's disease pathologies.

The second paper, "Developing Explainable Deep Model for Discovering Novel Control Mechanism of Neuro-Dynamics," [13] utilizes Partial Differential Equations (PDEs) to model the

dynamic and self-organized behaviors crucial for understanding Alzheimer's progression. This paper emphasizes the role of network topology in modeling the spread of pathological proteins like amyloid plaques and tau tangles. The approach proposes a reaction-diffusion process constrained by network topology, using advanced mathematical tools to simulate disease progression and offer potential control strategies.

Our third paper of interest, "Investigating hypotheses of neurodegeneration by learning dynamical systems of protein propagation in the brain," [14] critiques traditional diffusion models for simplifying the complex dynamics of protein propagation in neurodegenerative diseases. It proposes a more nuanced model that considers variable protein concentrations and their critical thresholds, which could lead to better simulations of disease progression and more accurate predictions of neurodegeneration patterns.

In the fourth paper, "Modeling and inference of spatiotemporal protein dynamics across brain networks, the focus shifts to integrating long-term biomarker dynamics with misfolded proteins' kinetics through a sophisticated modeling framework. This study leverages data-driven estimates to enhance the understanding of misfolded proteins' behavior over the disease's course, highlighting the challenges of modeling complex, high-dimensional systems in a disease context.

Finally, the fifth paper, "A physics-based model explains the prion-like features of neurodegeneration in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis," [16] adopts the Fisher–Kolmogorov equation to model the spread of misfolded proteins across the brain. This approach aligns with the prion paradigm, suggesting that misfolded proteins propagate in a manner similar to infectious agents, providing a compelling model for the nonlinear reaction and diffusion processes involved in neurodegeneration.

Each of these papers contributes uniquely to our understanding of Alzheimer's disease, collectively offering a comprehensive view of the current scientific landscape and future research directions in modeling neurodegenerative diseases.

IV. Dataset

A. Data Acquisition and Handling

We have successfully gained access to the ADNI dataset, a crucial resource for our Alzheimer's disease research. After completing the required CITI training, which is essential for working with the ADNI data, we obtained permission to download three key datasets: `ADNIMERGE_17Feb2024`, `UCBERKELEY_AMY_6MM_17Feb2024`, and `UCBERKELEY_TAUPVC_6MM_14Feb2024`. These datasets offer comprehensive amyloid and tau protein imaging data, which are essential for our analysis and modeling of Alzheimer's disease progression.

B. Unified Dataset

From the above three datasets, we have crafted a Unified Dataset. We extracted patient demographics, such as age, sex, and health information (including whether they carry the APOE4 gene and how many copies) and patients diagnosis, from `ADNIMERGE_17Feb2024`. This gene is associated with a higher risk of Alzheimer's disease. We used `UCBERKELEY_AMY_6MM_17Feb2024` to obtain Tau accumulation values in 80 brain regions, and `UCBERKELEY_TAUPVC_6MM_14Feb2024` to extract Amyloid-beta values for the same 80 brain regions as seen in Figure 1.

There is a unique RID 903 in `UCBERKELEY_TAUPVC_6MM_14Feb2024` with 1534 scans. We selected only patients with longitudinal data (meaning those with scans $\geq$ 2), leaving our Unified Dataset with 402 RIDs and 1032 scans. For `UCBERKELEY_AMY_6MM_17Feb2024`, we extracted amyloid values for the same patients and considered a scan valid if it was within a year of the Tau scan. After merging the datasets, we discarded any missing data, leaving our Unified Dataset with 236 RIDs and 588 scans. For all these patients, we extracted comprehensive demographic and health information, as seen in Figure 2.

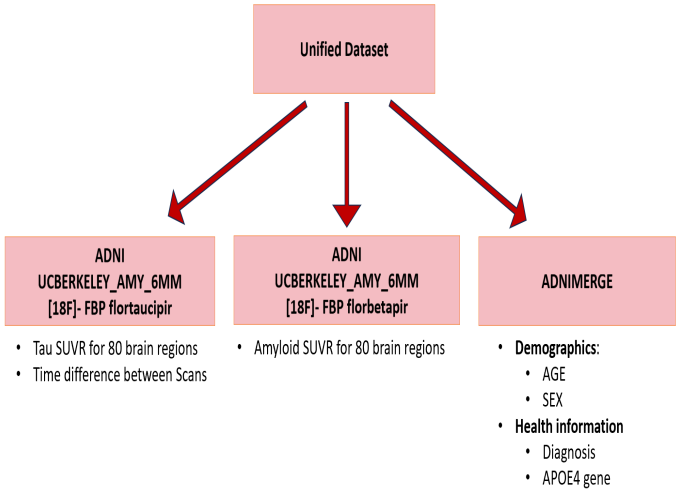

Fig. 1. Unified Dataset

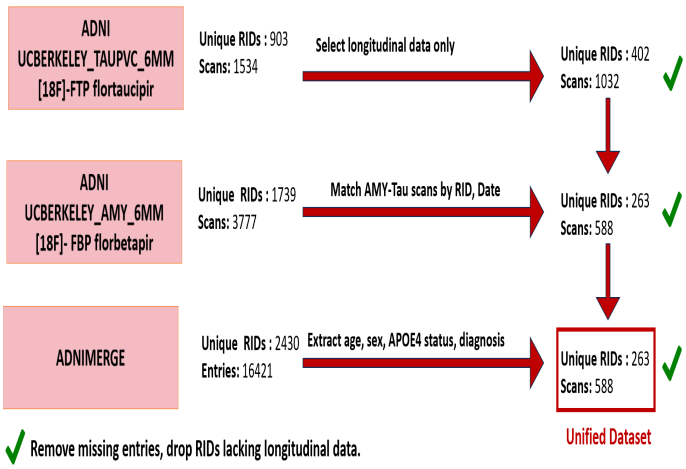

Fig. 2. Unified Dataset Creation

C. Data Handeling Remarks

In our study, we have prioritized maintaining high data quality and integrity throughout the research process. A crucial aspect of this effort involved the removal of any blank or missing (NaN) data from the dataset. By eliminating incomplete data points, we ensured that our analysis was based on accurate and reliable information, reducing potential biases that could arise from handling missing values through imputation or other methods.

We also took careful measures to prevent data leakage. Specifically, we ensured that the same Subject RID was either present in the training or testing set, but not both, across all data points. This strict separation between training and testing datasets was crucial to providing a realistic assessment of model performance and avoiding overly optimistic estimates that could arise from testing on data already seen during training.

In addition, we maintained a clear distinction between training and validation sets. The same Subject RID was included in either the training or validation set but never both. This practice allowed us to effectively validate our models' performance on unseen data, thereby providing a more accurate measure of their generalizability.

When employing cross-validation, we further ensured that each Subject RID was present in no more than one fold. This prevented data leakage between folds and ensured that our cross-validation results were not artificially inflated due to overlap between training and validation data.

Lastly, to avoid data leakage through feature standardization, we standardized features per fold, calculating the mean and standard deviation within each fold independently. This practice ensured that data from other folds did not influence the scaling of the features, thereby preserving the integrity of the cross-validation process.

By adhering to these principles of data handling, we aimed to provide a solid foundation for our research findings, minimizing biases and ensuring the reliability of our predictive models.

D. Data Stratifying

We stratified the data per diagnosis for both the inner and outer loops of our nested cross-validation process. This stratification was based on the following diagnostic categories: Cognitively Unimpaired (CU), Subjective Memory Complaints (SMC), Early Mild Cognitive Impairment (EMCI), Late Mild Cognitive Impairment (LMCI), and Alzheimer's Disease (AD) as seen in the figure below. By maintaining a proportional representation of all diagnostic categories in each fold, we ensured that model performance was evaluated more comprehensively and equitably across different clinical conditions. This approach helped to reduce biases due to uneven distribution and provided a realistic assessment of how the models would perform in a real-world diagnostic setting.

Stratifying by diagnosis is crucial because it ensures that both the training and testing sets reflect the actual distribution of diagnostic categories. This minimizes sampling bias by guaranteeing that each diagnostic group is proportionally represented across all folds. As a result, models are less likely to overfit to specific conditions or underperform in underrepresented categories. By maintaining this proportional representation, our models were evaluated more comprehensively, leading to realistic assessments of how they would perform in a real-world diagnostic setting.

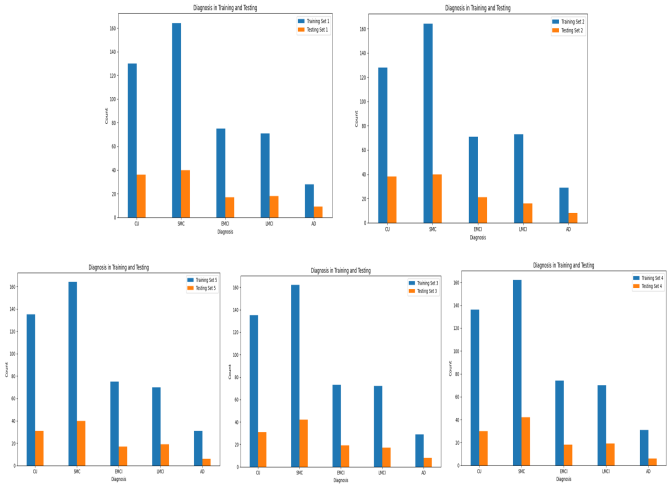

Fig. 3. Stratification of diagnostic groups across five outer folds: Cognitively Unimpaired (CU), Subjective Memory Complaints (SMC), Early Mild Cognitive Impairment (EMCI), Late Mild Cognitive Impairment (LMCI), and Alzheimer's Disease (AD).

Moreover, stratification enhances the clinical relevance of our models by mirroring the real-world clinical population. This approach allows for a more comprehensive evaluation of predictive accuracy across all stages of cognitive impairment, from Cognitively Unimpaired (CU) to Alzheimer's Disease (AD). As a result, it identifies where models excel and highlights conditions that require further improvement.

V. Results

The primary objective of this project was to predict tau protein accumulation values in 80 different brain regions using multilayer perceptrons. We employed a 5x5 nested cross-validation approach, selecting models in the inner loops and testing them on the outer loops. A comprehensive grid search was conducted to identify the optimal models with the lowest mean absolute error (MAE). Additionally, an ablation study was performed to evaluate the impact of different features on model performance.

A. Input Features

The input features for the models included 169 variables across the following categories:

- **Tau SUVR - Subcortical Regions**: 6 regions x 2 (right and left hemispheres)
- **Tau SUVR - Cortical Regions**: 34 regions x 2 (right and left hemispheres)
- **Amyloid-beta SUVR - Subcortical Regions**: 6 regions x 2 (right and left hemispheres)
- **Amyloid-beta SUVR - Cortical Regions**: 34 regions x 2 (right and left hemispheres)

- **Demographics and Genetic Information**:
  - Age
  - Sex
  - APOE4 status
- **Diagnosis Categories**:
  - Cognitively Unimpaired (CU)
  - Subjective Memory Concerns (SMC)
  - Early Mild Cognitive Impairment (EMCI)
  - Late Mild Cognitive Impairment (LMCI)
  - Alzheimer's Disease (AD)
- **Time Difference (t) Between Scans**: 1

In total, 169 candidate input features were identified. An ablation study was conducted to compare the predictive performance of models with various combinations of these features.

Grid Search Hyperparameters A comprehensive grid search was conducted to identify the optimal models with the lowest mean absolute error (MAE). The following hyperparameters were explored:

- **Activations**: `leaky_relu`, `elu`, `selu`, `swish`, `relu`
- **Learning Rates**: `[0.001, 0.01]`
- **Epochs**: `[200,400, 600, 800]`
- **Hidden Layers**: `[2, 3, 4]`
- **Neurons per Layer**: `[16, 32, 64, 128]`

Some of the best MAE models had the following parameters: activation functions `leaky_relu` and `elu`, learning rate of `0.001`, 600 epochs, 4 hidden layers, and varying numbers of neurons per layer. For instance, one model used `leaky_relu` with 32 neurons per layer, while another used `elu` with 128 neurons per layer.

These models effectively balanced the choice of activation functions, number of hidden layers, and neurons per layer, leading to robust performance in predicting tau accumulation.

After selecting the optimal models in the inner loop of the cross-validation process, these models were tested on the outer loop test sets. The predictions from each model were averaged to compute the Mean Absolute Error (MAE). By leveraging this nested cross-validation approach, we ensured robust performance evaluation and minimized the risk of overfitting. The comprehensive evaluation across multiple outer folds provided reliable performance estimates, ultimately highlighting the predictive capabilities of the selected models. In addition to evaluating overall performance, we further assessed the impact of different feature sets through an ablation study and analyzed the feature importance to better understand the influence of specific predictors.

B. Model Performance

Ablation Study Results The ablation study compared the capabilities of different models in predicting tau accumulation values, including:

- **Model 1**: Tau, Amyloid-beta levels (Amy), and t.
- **Model 2**: Tau, Amyloid-beta levels (Amy), demographics, patient health data, and t.
- **Model 3**: Tau and t only.

The study revealed the importance of specific feature sets in predicting tau accumulation.

C. Discussion

The results demonstrate that multilayer perceptrons can effectively predict tau protein accumulation in the brain. Our grid search and nested cross-validation approach ensured that the models selected had robust predictive performance across different outer folds. The ablation study and feature importance analysis underscore the significance of demographic and regional connectivity features in accurately predicting tau accumulation. However, Figures 4 to 8 showed some outliers that require further inspection. These outliers could be due to noise or other factors not accounted for in our models. Therefore, in our future work, we plan to discuss and implement noise assessment to identify and handle such outliers.

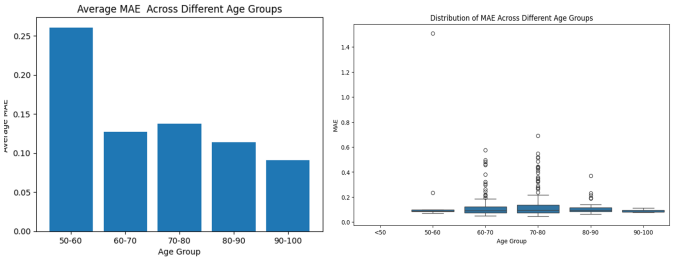

Fig. 4. MAE Across Age Groups (Tau+Amy+Demo+Δt)

Figure 4 shows the MAE for Model 2 across different age groups remained consistent; however, within the age group younger than 50, we noticed an increase in error. This increase in error reflects the challenges of predicting Alzheimer's disease in younger individuals due to various factors that cannot be easily captured by the model. Younger individuals often present greater variability in their clinical presentation, progression, and risk factors, making it difficult for the model to accurately predict tau protein accumulation. Further research is needed to address these challenges, possibly by incorporating additional features or improving data representation for this demographic group.

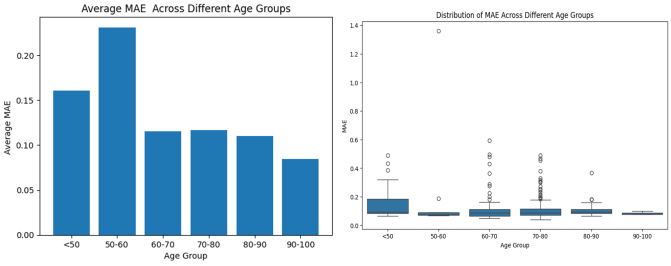

Fig. 5. MAE Across Age Groups (Tau+Δt)

Similarly, Model 1 performed the same, as shown in Figure 5. Despite consistent MAE across most age groups, the age group younger than 50-60 exhibited a noticeable increase in error, highlighting the complexity of predicting Alzheimer's disease in this demographic group.

Model 3 also demonstrated similar behavior, as shown in Figure 6. Although the MAE remained stable across most age groups, the age group younger than 50 showed an increase in

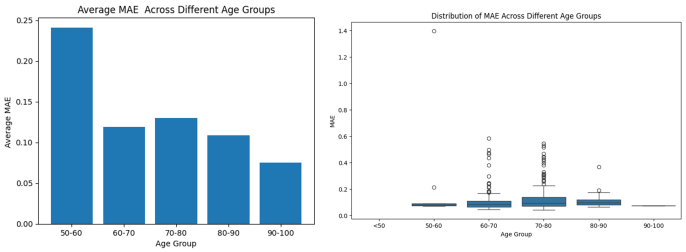

Fig. 6. MAE Across Age Groups (Tau+Amy+Δt)

error, emphasizing the need for improved data representation or additional features to better capture the variability in younger individuals.

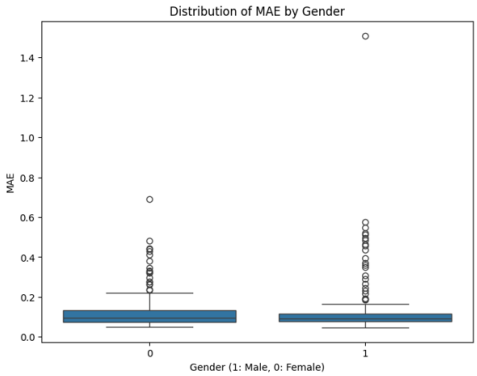

Fig. 7. MAE Across Sex Groups (Tau+Amy+Demo+Δt)

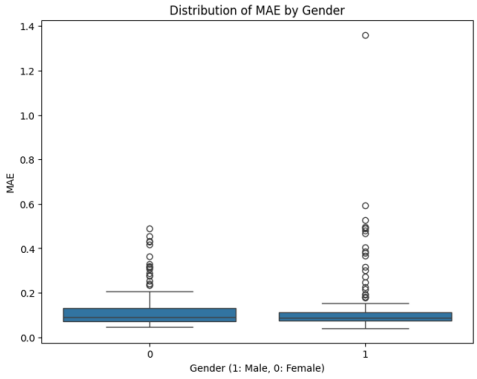

Fig. 8. MAE Across Sex Groups (Tau+Δt)

The Mean Absolute Error (MAE) across sex groups for all three models showed no statistically significant differences between male and female groups, as shown in Figures 7, 8, and 9. This suggests that the models performed consistently regardless of sex, indicating that sex is not a significant factor affecting the prediction of tau protein accumulation in this context

We studied the Mean Absolute Error (MAE) for the three models across different APOE4 gene groups: 0 copies, 1 copy, and 2 copies. As shown in Figures 10, 11, and 12, we noticed an increased MAE for patients with two copies of the APOE4 gene. This increase is likely related to the higher genetic risk of

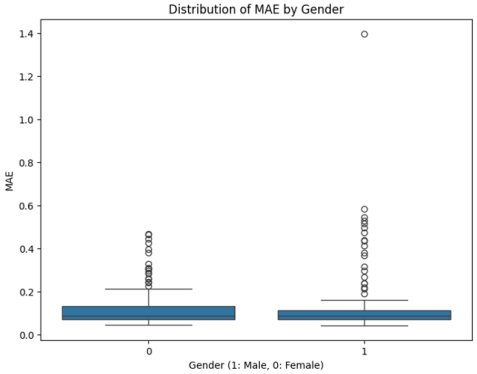

Fig. 9. MAE Across Sex Groups (Tau+Amy+Δt)

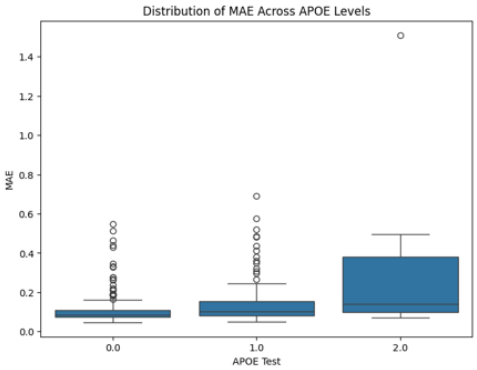

Fig. 10. MAE Across APOE4 Values (Tau+Amy+Demo+Δt)

developing Alzheimer's disease (AD) associated with carrying two copies of the APOE4 allele.

Patients with two copies of APOE4 have a significantly higher risk of developing AD compared to those with 0 or 1 copy. The presence of two APOE4 alleles accelerates amyloid-beta accumulation, tau pathology, and neurodegeneration, leading to more pronounced cognitive decline. The increased variability in disease progression and severity among individuals with two copies of APOE4 makes predicting tau accumulation more challenging, thus resulting in higher prediction errors.

This finding underscores the importance of incorporating genetic information, such as APOE4 status, into predictive models to improve accuracy. However, it also highlights the need for further refinement in predictive modeling for individuals with increased genetic risk to account for the variability in AD progression.

The results demonstrate that multilayer perceptrons has the potential tp predict tau protein accumulation in the brain. Our grid search and nested cross-validation approach ensured that the models selected had robust predictive performance across different outer folds. The ablation study and feature importance analysis underscore the significance of demographic and regional connectivity features in accurately predicting tau accumulation.

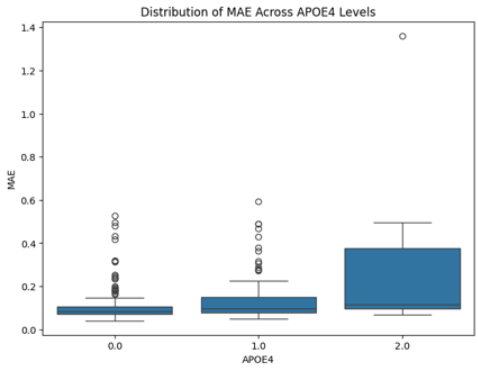

Fig. 11. MAE Across APOE4 Values (Tau+Δt)

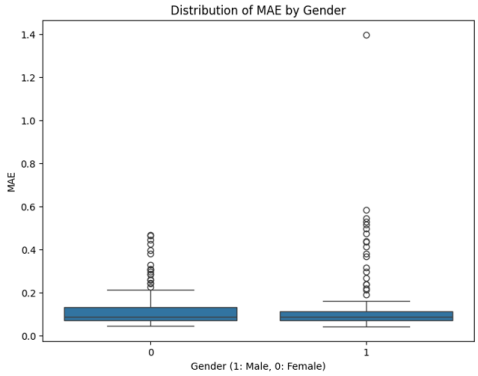

Fig. 12. MAE Across APOE4 Values (Tau+Amy+Δt)

VI. Conclusion

Multilayer perceptrons have demonstrated promising predictive performance for tau protein accumulation in the brain. We utilized a grid search and nested cross-validation approach, ensuring robust predictive performance across different outer folds. An ablation study and feature importance analysis revealed the significance of demographic and regional connectivity features in accurately predicting tau accumulation. However, our results identified outliers that require further inspection, particularly in younger age groups and patients carrying two copies of the APOE4 gene. Future work aims to enhance noise assessment and refine predictive models to address these discrepancies effectively.

Figures 4 to 12 showed increased prediction errors in individuals younger than 50, highlighting challenges in predicting Alzheimer's disease in this demographic. Additionally, increased mean absolute error (MAE) was observed among patients with two copies of the APOE4 gene, emphasizing the importance of incorporating genetic information into predictive models. These findings underline the potential of multilayer perceptrons and the need for further refinement to account for genetic variability and age-related complexity in Alzheimer's disease progression.

VII. Future Work

In future research, we aim to build upon our study by refining the methodology for measuring noise within our dataset. This will involve calculating the Tau SUVR mean for each distinct brain region and establishing a noise threshold, typically set at 10% above the calculated mean. This threshold will serve as a valuable benchmark for identifying noisy data points within the dataset. We will quantify the percentage of noise by dividing the total number of data points surpassing the threshold by the total dataset size. This approach will systematically evaluate the impact of noise across the dataset. By incorporating this knowledge, we plan to enhance the accuracy and reliability of our subsequent data analyses and interpretations, providing a solid foundation for future research findings.

Furthermore, we aim to apply Fourier Features mapping to our dataset. This approach may lead to improved Tau prediction by capturing high-frequency components that could be present in the dataset but remain undetected through conventional methods. Fourier Features mapping introduces periodic patterns that help neural networks approximate high-frequency functions more effectively. By capturing subtle variations and complex patterns, this technique could provide a more nuanced understanding of Tau accumulation and its relationship to other factors. Leveraging Fourier Features may thus significantly improve the predictive accuracy and reliability of our models, offering deeper insights into the nature of Tau pathology.

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