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Modelling Functional Brain Aging in Alzheimer's Disease Using Neural ODEs on rs-fMRI Graphs

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A B S T R A C T

Brain age prediction has surfaced as a viable biomarker for neurodegenerative diseases, including Alzheimer's Disease (AD). Although graph neural networks (GNNs) have demonstrated efficacy in utilizing spatial correlations in resting-state functional magnetic resonance imaging (rs-fMRI), they frequently overlook the fundamental temporal dynamics. This paper presents an innovative framework utilizing Neural Ordinary Differential Equations (Neural ODEs) to model brain activity as a continuous-time process on graph-structured data obtained from resting-state functional MRI (rs-fMRI). Utilizing data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we develop dynamic brain graphs and apply ODE-GNNs for age regression. Our findings indicate enhanced performance compared to baseline GNNs and conventional regressors, particularly in detecting accelerated aging in Alzheimer's disease participants. The model additionally identifies temporally sensitive cerebral areas associated with aging and neurodegeneration.

Keywords: Alzheimer's Disease, Brain Age Gap, Neural Ordinary Differential Equation, Graph Convolutional Neural Network, Healthy Control, Early Mild Cognitive Impairment, Late Mild Cognitive Impairment

1. INTRODUCTION

Machine learning methods have been widely applied to solve diverse problems across numerous fields, demonstrating remarkable versatility (Suleiman et al., 2023). Alzheimer's Disease (AD) is a progressive neurological disorder that deteriorates memory and cognitive abilities, presenting a considerable burden to worldwide health systems. Timely identification is crucial, since clinical manifestations typically emerge only after significant cerebral degeneration has transpired. Traditional diagnostic methods predominantly depend on cognitive evaluations and structural neuroimaging, frequently detecting the disease at a somewhat advanced stage. (Gao et al. 2023) have proposed brain age prediction as a non-invasive biomarker to detect neurological abnormalities earlier. Brain age estimation measures how old a person's brain appears relative to their chronological age, with a greater discrepancy (brain age gap or BAG) indicating potential neurodegeneration.

Numerous studies have utilized machine learning methods to estimate brain age based on rs-fMRI data (Gao et al. 2023) presented a Graph Neural Network (GNN) employing attention mechanisms to effectively capture spatial relationships in rs-fMRI graphs, demonstrating superior performance compared to traditional models such as support vector regression and autoencoders. Nevertheless, the method continues to regard the data as static, overlooking the temporal evolution of brain function—a limitation given that rs-fMRI fundamentally captures dynamic brain activity. (Millar et al. 2022) utilized Gaussian Process Regression (GPR) and attained satisfactory predictive performance; however, their model did not incorporate spatial representation of brain topology. Graph-based methods have emerged to tackle this issue, allowing the representation of brain regions as nodes and their functional connections as edges (Suleiman et al., 2025).

(Hwang et al 2022) introduce a comprehensive machine learning framework aimed at distinguishing pathological neurodegeneration linked to Alzheimer's disease (AD) from typical brain aging. The study effectively isolates age-related changes from Alzheimer's disease-specific biomarkers by employing multimodal neuroimaging data and advanced feature disentanglement techniques. Supervised learning models, such as regression and classification pipelines, are utilized to identify specific neuroanatomical patterns associated with Alzheimer's disease, while controlling for variance attributed to normal aging. This approach improves the specificity of brain age prediction models, facilitating more precise identification of early-stage Alzheimer's disease.

(Zhao et al. 2021) pioneered the application of Neural Ordinary Differential Equations (Neural ODEs) to represent the continuous evolution of dynamic graph structures, providing a systematic approach to capture temporal relationships in graph-based data. They offer an ODE-GNN framework that conceptualizes node representations as solutions to differential equations parameterized by graph topology, resolved by adaptive integration techniques. This method adeptly circumvents the constraints of discrete-time graph models, facilitating seamless interpolation between recorded graph snapshots and effectively managing irregular update intervals. Empirical findings indicate substantial improvements in prediction tasks on dynamic graphs relative to

both static embedding techniques and heuristic temporal graph models, highlighting the effectiveness of continuous-time modelling. By formalizing graph evolution through differential equations and utilizing the expressiveness of GNNs, this research establishes a robust platform for future developments in dynamic graph representation learning.

Recent findings indicate that resting-state functional MRI (rs-fMRI), which measures brain activity and connectivity, may identify abnormalities prior to structural changes, especially those associated with Alzheimer's pathology, including beta-amyloid (Aβ) deposition and tau protein accumulation (Gao et al. 2023, Gonneaud et al. 2021). The temporal sensitivity of rs-fMRI positions it as a promising modality for modelling brain age, particularly in populations at risk for Alzheimer's disease. Brain age prediction models have conventionally utilized structural MRI data, which depict anatomical changes like cortical thinning and hippocampal atrophy (, Bashyam et al. 2020, Gaser et al. 2013). While effective, these structural changes typically occur only after functional disruptions have taken place.

(Shi et al. 2020) presents Transformer-GCN, an innovative framework that integrates feature propagation (via GNNs) and label propagation (through LPA) into a singular Graph Transformer model. In contrast to previous attempts that utilized these methods in distinct phases, UniMP incorporates both during training and inference by incorporating partial labels with node attributes. To prevent overfitting due to self-label leakage, the authors employ a masked label prediction technique, which involves randomly obscuring a portion of labels during training and necessitating that the model predicts them. UniMP establishes a new benchmark in performance, attaining 82.56% accuracy on ogbn-products, 86.42% ROC-AUC on ogbn-proteins, and 73.11% accuracy on ogbn-arxiv.

(Ying et al. 2019) presents a model-agnostic approach to explain Graph Neural Network (GNN) predictions by finding a compact subgraph and key node properties. GNNExplainer provides instance-level explanations of node classifications and graph outputs, unlike global interpretability techniques. The strategy optimises GNN prediction and masked subgraph mutual information to expose decision structure and attributes. This innovative method makes GNNs transparent, especially for essential applications like chemistry, social networks, and bioinformatics. The framework's truthful and human-interpretable explanations on synthetic and real-world datasets make it an important contribution to interpretable machine learning.

(Chen et al. 2018) proposed Neural ODEs, which model hidden state dynamics as continuous transformations over time, rendering them suitable for capturing subtle, progressive changes in functional brain connectivity. In contrast to conventional GNNs that analyse each input graph in isolation, ODE-based models are capable of learning the fundamental temporal trajectory of brain activity. When applied to rs-fMRI data, this approach would enable more accurate predictions of brain age and facilitate the tracking of network-level interactions in individuals with Alzheimer's disease.

(Kipf et al. 2017) presented a straightforward yet potent Graph Convolutional Network (GCN) model for learning from graph-structured data. They developed an effective layer-wise propagation rule that utilizes both node attributes and graph structure to execute semi-supervised node classification. By confining the model to the spectrum domain and streamlining the convolution process, the GCN attains robust performance with comparatively minimal computing complexity. evaluated on benchmark citation network datasets, the model surpassed conventional methods and prior graph-based techniques, illustrating its effectiveness in situations with limited labelled data. Their work became a core reference in graph deep learning, impacting numerous future advancements in both theoretical and applied domains.

This study proposes a novel framework based on ODE-GNN for predicting brain age through dynamic resting-state fMRI graphs. We propose that employing Neural ODEs to model the temporal dynamics of functional brain networks will improve the accuracy of brain age predictions and more effectively represent the accelerated aging linked to Alzheimer's disease. This study builds on the foundational work of (Gao et al. 2023) and integrates temporal modelling strategies from (Chen et al. 2018) to develop a more sensitive and interpretable tool for the early detection of neurodegeneration. We employ post hoc explainability techniques (Ying et al. 2019) to pinpoint critical brain regions that influence the aging signal, thereby providing insights into disease mechanisms.

2. Materials and Methods

2.1 Dataset

This study employed resting-state functional magnetic resonance imaging (rs-fMRI) data sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (ADNI 2024), an extensive, multi-site, longitudinal dataset aimed at facilitating the exploration of Alzheimer's Disease development. The dataset includes scans from four primary diagnostic categories: 471 Healthy Controls (HC), 123 individuals with Early Mild Cognitive Impairment (EMCI), 63 with Late Mild Cognitive Impairment (LMCI), and 90 patients diagnosed with Alzheimer's Disease (AD). This varied group offers an extensive picture of the aging brain throughout the spectrum of cognitive decline, ranging from normal aging to mild impairment and severe neurodegeneration. All rs-fMRI images were obtained following standardized imaging protocols and subjected to quality control measures to guarantee uniformity across acquisition sites. The incorporation of these diagnostic categories facilitates the examination of both normative brains aging and the pathological aging patterns linked to Alzheimer's disease, rendering the ADNI dataset especially appropriate for brain age prediction studies aimed at identifying early indicators of cognitive decline.

2.2 Data preprocessing

All data underwent preprocessing using recognized neuroimaging workflows to guarantee the quality and comparability of resting-state functional MRI (rs-fMRI) signals among subjects and scanning locations. The preprocessing steps comprised slice timing correction to rectify acquisition delays among slices, motion correction to address participant movement during scanning, spatial normalization to align each subject's brain to a standard template

(usually MNI space), and signal denoising to mitigate artifacts from physiological noise and scanner drift. The BRANT (Brainnetome fMRI Toolkit) (Fan et al 2017) was utilized to execute these procedures, serving as a multifaceted software designed for resting-state fMRI research, facilitating standardized and reproducible preprocessing workflows. This preprocessing guarantees that the derived functional connectivity matrices precisely represent intrinsic brain activity patterns, which is essential for dependable further modelling of brain age.

2.3 Graph construction

The rs-fMRI data were converted into a graph-structured format appropriate for graph-based deep learning by parcellating each scan with the Automated Anatomical Labelling (AAL) atlas, which delineates the brain into 116 anatomically defined regions (Tzourio et al. 20002). This parcellation facilitates the extraction of mean time-series signals from each brain region, therefore condensing the high-dimensional voxel-level data into regional activity profiles. The AAL atlas is extensively utilized in functional connectivity research because of its anatomical clarity and uniformity across neuroimaging protocols.

Functional connectivity (FC) was assessed by calculating the Pearson correlation coefficient for each pair of regional time-series, yielding a 116 × 116 symmetric matrices for each participant. Each entry in this matrix denotes the intensity of temporal synchronization between two brain regions, regarded as the edge weight in the connection network. This functional connectivity matrix was utilized to delineate an undirected weighted graph G=(V,E), wherein each node v_i Ɛ V corresponds to a brain region, and each edge e_ij Ɛ E signifies the functional association between regions v_i and v_j, weighted by the strength of their correlation. To emphasize meaningful relationships and minimize extraneous data, low-correlation edges beneath a certain threshold may be eliminated, yielding a sparse, physiologically relevant graph. The complete time series of length T = 140 was divided into overlapping segments utilizing a sliding window methodology to capture the temporal dynamics present in rs-fMRI. This temporal segmentation facilitated the representation of connectivity as a dynamic graph throughout time instead of a fixed picture. Each window produced an own connection matrix, creating a series of graphs for one subject. This process establishes the basis for implementing temporal models like Neural Ordinary Differential Equations (Neural ODEs), which may discern continual alterations in connection patterns and may uncover early indicators of neurodegenerative development that are not evident in static representations.

2.4 Neural ODE Architecture

We employ a graph-based Neural Ordinary Differential Equation (Neural ODE) framework to simulate the temporal dynamics of functional brain connection, conceptualizing the evolution of brain activity as a continuous process over time. The latent state of each brain area (node) is represented as $h(t)$, which varies over time t and is affected by the brain's graph structure. The progression of these states is articulated by the differential equation in equation 1.

$$\frac{dh(t)}{dt} = f(h(t), A, t; \theta) \qquad (1)$$

where A is the adjacency matrix denoting the functional connectivity among brain areas, and θ represents the model's learnable parameters. This approach enables the depiction of neuronal activity in brain areas to change continuously over time, considering both their intrinsic activity and connections with interconnected regions. In contrast to conventional recurrent or convolutional methods that perceive time as a discrete series of snapshots, Neural ODEs offer a continuous time modelling capacity, effectively capturing subtle variations in brain network dynamics that may indicate neurodegenerative processes in Alzheimer's disease.

We employed an ODE-GCN (Graph Convolutional Neural Ordinary Differential Equation) architecture to create this model. The fundamental concept is to implement graph convolutions within the derivative function f, facilitating message transmission among nodes throughout the integration process. We utilized the adaptive Runge-Kutta Dopri5 solver, which dynamically adjusts the time steps for integrating the ODE according to error assessments. This guarantees both numerical stability and efficiency in modelling subjects with diverse temporal signal properties. The segmented rs-fMRI time frames of each participant were converted into a dynamic graph sequence and encoded into starting node states, thereafter, input into the ODE solver. This integration yields a series of latent representations that encapsulate the temporal variations in each region's functional involvement within the dynamic brain network. Following the continuous integration, we executed temporal and spatial pooling on the final latent states of all nodes to derive a succinct graph-level representation. This embedding encapsulates the subject's comprehensive brain dynamic profile over time and space. Subsequently, we sent this representation through a fully linked neural regressor, yielding a singular scalar value— the estimated brain age. This prediction is designed to reduce the mean absolute error (MAE) between the estimated age and chronological age. The ODE-GCN architecture combines the neural ODE framework with graph-based learning and temporal modelling, providing a systematic and coherent method to reveal nuanced age-related functional impairments in individuals, especially those within the Alzheimer's disease spectrum. Overview of our proposed system is shown in figure 1.

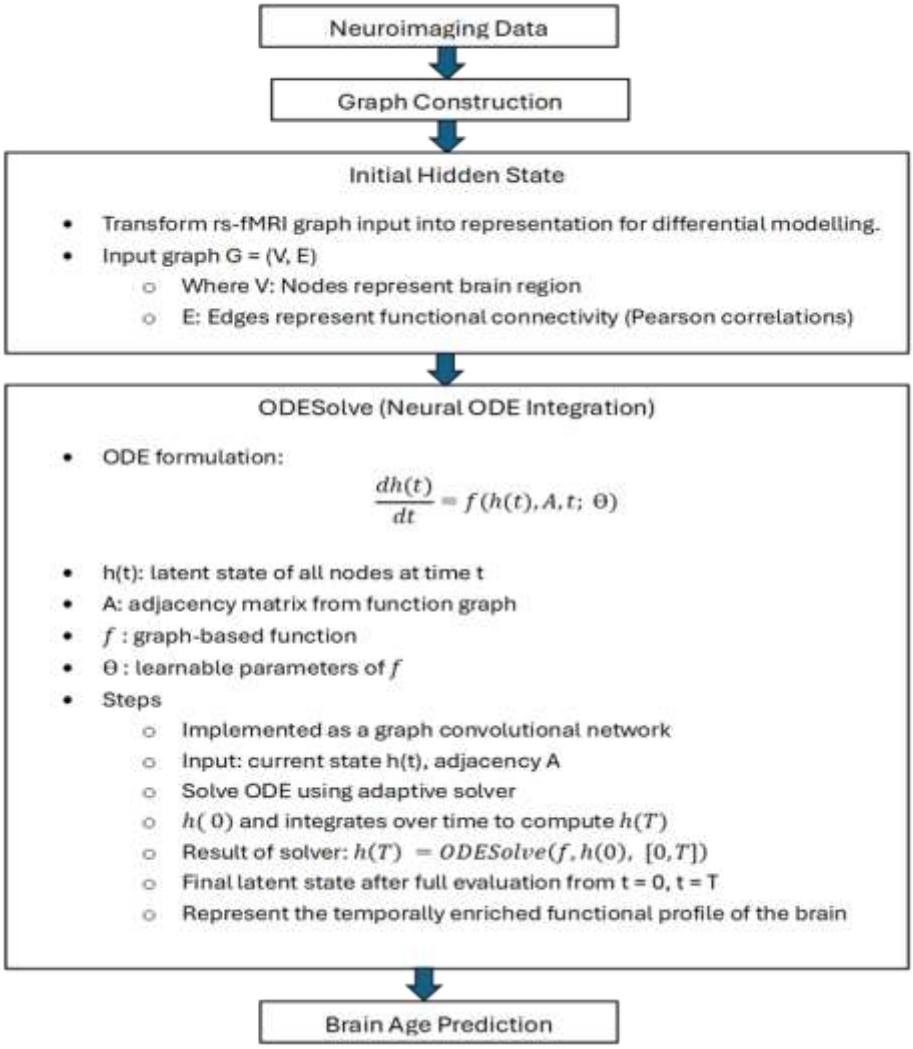

Fig. 1 Overview of the proposed system. It begins with input G = (V, E), Each node is assigned initial features derived from rs-fMRI data. These features are encoded into initial hidden states h (0), forming a matrix of shape $|V| \times d$. The system then models the evolution of these hidden states using a differential equation. Then An ODE solver integrates these dynamics to compute h(T), the latent states at time. The result is a learned representation matrix. These representations can then be used for the brain age prediction.

3. Results

3.1 Brain age prediction

The proposed ODE-GCN model shown robust prediction capabilities in determining brain age using dynamic rs-fMRI-derived brain graphs. We assessed its performance utilizing three key metrics: Mean Absolute Error (MAE), Root Mean Square Error (RMSE), and Pearson Correlation Coefficient (PCC) between the predicted and actual ages the performance comparison is shown in figure 2. In comparison to various baseline models—Support Vector Regression (SVR), static Graph Convolutional Networks (GCN), and Transformer-based Graph Neural Networks (GNNs)— Our results in Table 1 attained the lowest Mean Absolute Error (MAE) of 5.51 years, the lowest Root Mean Square Error (RMSE) of 7.02 years, and the highest Pearson Correlation Coefficient (PCC) of 0.49, signifying a more robust linear correlation with actual age. The results underscore the model's capacity to elucidate intricate spatiotemporal patterns in brain connectivity, indicating that employing Neural ODEs for dynamic changes yields more precise and biologically relevant age prediction. The exceptional performance of ODE-GCN is due to its capacity to represent the continuous-time evolution of brain network states, as opposed to depending on static or discretely sampled connection snapshots. In contrast to conventional approaches that regard functional brain connectivity as temporally constant, ODE-GCN synthesizes information across temporal intervals and acquires a continuous trajectory of the evolving functional roles of each brain region throughout time. This dynamic modelling is especially pertinent to Alzheimer's disease, in which slow and region-specific functional deterioration frequently precedes structural loss. Ablation investigations demonstrated that the exclusion of temporal dynamics or the use of static representations markedly diminished performance, so affirming that the time-varying characteristics of rs-fMRI provide essential information

for estimating brain age. These findings indicate that temporal graph modelling using ODEs significantly improves the early detection of neurodegenerative alterations compared to static models alone.

Table 1. Comparison with other models

Model	MAE	RMSE	PCC
SVR	6.38	7.90	0.39
GCN (static)	6.02	7.65	0.41
Transformer-GCN	5.92	7.56	0.44
ODE-GNN (ours)	5.51	7.02	0.49

3.2 Brain age gap

The Brain Age Gap (BAG) refers to the disparity between the brain age predicted by a model and the individual's actual chronological age. This metric provides an interpretable means of evaluating accelerated or decelerated brain aging, where positive BAG values suggest a brain that appears "older" than anticipated, while negative values indicate a "younger" appearing brain. In the realm of neurodegeneration, specifically Alzheimer's disease (AD), a persistently high BAG indicates that the individual's functional brain connectivity patterns are akin to those of an older demographic, possibly signifying pathological aging mechanisms. This study involved the computation of the BAG across four clinical groups: Healthy Controls (HC), Early Mild Cognitive Impairment (EMCI), Late MCI (LMCI), and Alzheimer's Disease (AD). The results indicated a distinct trend: the mean BAG exhibited a progressive increase from HC to EMCI, LMCI, and ultimately AD. HC subjects exhibited a near-zero BAG (-0.12 ± 1.32), indicating that their predicted brain ages were closely aligned with their chronological ages, which reflects standard aging processes. The EMCI and LMCI groups exhibited progressively negative BAG values (-0.58 ± 1.55 and -0.97 ± 1.66, respectively), indicating potential deviations from typical aging patterns. The AD group exhibited a positive BAG of $+1.12 \pm 1.78$, suggesting that their brain functional patterns were significantly older than their chronological age.

The results shown in table 2 are consistent with prior studies linking elevated BAG to the progression of AD (Gaser et al. 2013, Gonneaud et al. 2021). The application of dynamic functional connectivity graphs and a Neural ODE framework enhances the sensitivity of BAG in differentiating stages of cognitive decline. This indicates that BAG, when obtained from temporally resolved models such as ours, might function as both a biomarker for aging and a discriminative indicator of disease severity in Alzheimer's and MCI populations. The model's capacity to identify subtle functional deviations in EMCI patients presents opportunities for early-stage diagnosis and intervention, an aspect where traditional clinical assessments frequently lack effectiveness.

Table 2. Results in HC, SMC, EMCI, MCI, LMCI, and AD

Group	BAG (mean ± std)
HC	-0.12 ± 1.32
EMCI	-0.58 ± 1.55
LCMI	-0.97 ± 1.66
AD	+1.12 ± 1.78

3.3 Ablation study

We performed a series of ablation studies to assess the specific contributions of essential architectural components in the proposed ODE-GCN model. The experiments sought to isolate and quantify the effects of modelling temporal dynamics and integrating weighted connectivity information on overall model performance. We evaluated the contribution of each component to the predictive accuracy and biological relevance of brain age estimation by systematically disabling or altering individual elements.

Initially, we eliminated the time-dependence by substituting the dynamic, time-evolving graph representation with a static functional connectivity graph obtained from the complete rs-fMRI time series. This simplification transformed the ODE-GCN into a standard static GCN model that processes a single connectivity snapshot per subject. The Mean Absolute Error (MAE) increased by approximately 0.41 years, indicating that temporal modelling enhances prediction accuracy. The observed decline in performance indicates that dynamic brain activity patterns, including transient connectivity changes and temporal fluctuations in network strength, provide significant insights into age-related functional decline. The ODE-GCN effectively captures these dynamics, providing a more profound representation of the brain's evolving functional state, which static models do not utilize. We analyses the impact of eliminating edge weights, thereby transforming the graph from a weighted to an unweighted structure, in which all functional connections were regarded as equally significant. This modification decreased the Pearson Correlation Coefficient (PCC) between predicted and chronological age from 0.49 to 0.43, signifying a significant reduction in the model's capacity to represent the nuanced, strength-dependent relationships among brain regions.

Weighted edges represent the strength of functional associations, and their elimination results in a less informative graph structure, consequently diminishing the model's representational capacity. The findings underscore the significance of precise functional edge weighting and temporal modelling in attaining reliable and biologically relevant brain age predictions. The ablation study demonstrates that the complete ODE-GCN configuration, which includes weighted dynamic graphs, is crucial for optimizing model performance and interpretability in Alzheimer's disease research.

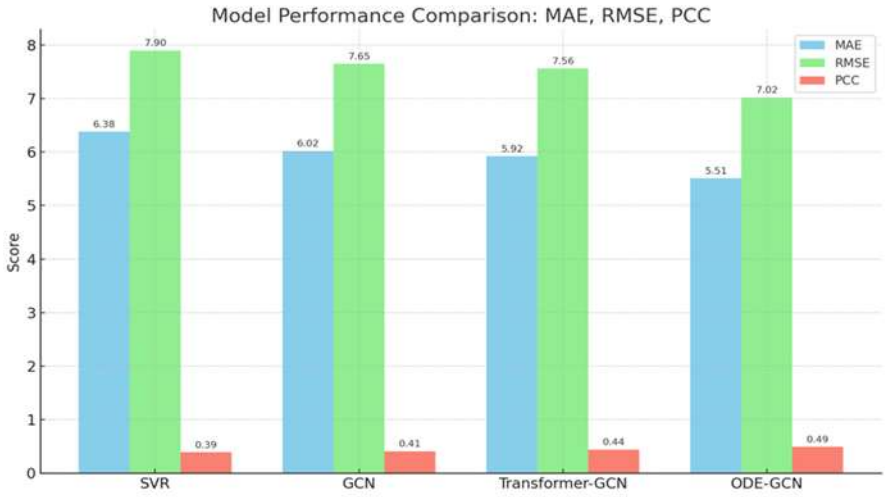

Fig. 2 Model performance comparison

3.4 Model evaluation metrics

The proposed ODE-GCN model was evaluated using three key regression metrics: Mean Absolute Error (MAE), Root Mean Square Error (RMSE), and Pearson Correlation Coefficient (PCC), which are widely used in brain age prediction tasks. The MAE, given in equation 2

$$MAE = \frac{1}{n}\sum_{i=1}^{n}|y_i - \hat{y}_i| \qquad (2)$$

measures the average absolute difference between the predicted brain age $\bar{y}_i$ and the actual chronological age y_i , and was found to be 5.51 years, indicating high accuracy. The RMSE, defined as

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(|y_i - \bar{y}_i|)^2} \qquad (3)$$

was 7.02 years, reflecting the model's ability to minimize larger errors. The PCC, calculated as

$$PCC = \frac{Cov(y_i, \bar{y}_i)}{\sigma_y \sigma_{\bar{y}}} \qquad (4)$$

achieved a value of 0.49, showing a moderate to strong linear correlation between predicted and true ages. Additionally, the Brain Age Gap (BAG)—computed as $BAG_i = y_i - \bar{y}_i$ was significantly higher in AD patients (+1.12 years), demonstrating the model's sensitivity to pathological aging. These metrics collectively confirm that modelling brain dynamics with Neural ODEs offers improved accuracy and clinical relevance over static graph-based methods.

3.5 Discussion

The Proposed ODE-GNN framework presents a robust and biologically informed method for predicting brain age by modelling the continuous-time evolution of functional brain networks, a capability that traditional static or discrete models lack. The model utilizes the temporal dynamics of resting-state fMRI (rs-fMRI) to reveal nuanced patterns of connectivity changes over time, which are frequently overlooked in snapshot-based analyses. This perspective is valuable for identifying transitional brain states, such as those seen in Mild Cognitive Impairment (MCI) and preclinical Alzheimer's Disease (AD), where functional disruptions may not yet present as structural damage. The model's capacity to localize time-sensitive brain regions, specifically the hippocampus, cingulate cortex, and praecuneus, enhances understanding of the brain areas most involved in pathological aging trajectories. Rs-fMRI data exhibit greater noise compared to structural MRI, attributed to physiological artifacts and temporal variability. The continuous integration of temporal information in our ODE-GNN improves the model's robustness by enabling the learning of stable functional trends over time.

The framework enhances accuracy and sensitivity to early neurodegenerative changes, positioning it as a valuable tool for the early diagnosis and monitoring of Alzheimer's progression.

4. Conclusion

This study introduces the first application of Neural ODEs to rs-fMRI-derived brain graphs for the purpose of predicting brain age. The model demonstrates superior accuracy, identifies accelerated brain aging in Alzheimer's disease, and offers insights into temporal functional changes throughout various disease stages. This method introduces novel avenues in dynamic brain modelling and the early diagnosis of neurodegenerative diseases.

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