Hybrid 3D CNN and ResNet Deep Transfer Learning for High-Resolution Hippocampal Atrophy Mapping and Automated Alzheimer's MRI Diagnosis

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ABSTRACT

Early and accurate detection of Alzheimer's disease (AD) is crucial for a timely clinical intervention. Atrophy of the hippocampus has been established as a key neurodegenerative biomarker. This study presents a Hybrid 3D CNN–ResNet model for automated hippocampal segmentation and dementia classification using high-resolution MRI scans. The proposed framework integrates 3D U-Net-based hippocampal segmentation with multi-scale feature extraction and deep residual learning, enabling a precise atrophy quantification and robust classification across the AD stages. A standardized preprocessing pipeline, incorporating NIfTI conversion, spatial normalization, denoising, and contrast enhancement, ensures consistency across multi-site datasets. The model was optimized using AdamW, Cyclical Learning Rate (CLR), and early stopping, achieving 97.31% classification accuracy and a 92.84% Dice Similarity Coefficient (DSC) for hippocampal segmentation. Grad-CAM and SHAP-based

interpretability confirm the biologically meaningful feature representations, aligning with established hippocampal atrophy patterns in AD progression. The external validation on the OASIS dataset demonstrated strong generalization, with only a 2.3% accuracy reduction, underscoring the model's robustness and clinical applicability. These findings establish the proposed approach as an effective and interpretable deep learning framework for early AD diagnosis and longitudinal disease monitoring.

Keywords-Alzheimer's disease; hippocampal atrophy; hybrid 3D CNN–ResNet; deep learning; MRI segmentation; multi-scale feature extraction; dementia classification

I. INTRODUCTION

AD represents a growing global health crisis, characterized by irreversible cognitive decline [1]. Its escalating prevalence, with projections indicating a near doubling every 20 years from the current 55 million cases, and the immense economic burden necessitate the urgent development of robust, accurate, and scalable diagnostic methodologies for timely intervention [2, 3]. Progressive hippocampal atrophy, a crucial brain structure for memory, serves as a key neuropathological hallmark and an early detectable biomarker for AD via neuroimaging [4, 6]. However, the current manual methods for assessing the hippocampal volume are labor-intensive, inconsistent, and limit the clinical utility [5]. This underscores the need for automated, reliable, and high-throughput techniques for precise quantification of this atrophy [7]. To address this diagnostic challenge, the present work proposes a novel Hybrid 3D CNN and ResNet deep transfer learning architecture for high-resolution hippocampal atrophy mapping and AD automated diagnosis from structural MRI. The framework integrates 3D CNNs for capturing the volumetric features and ResNet-based transfer learning to capture the very high-level discriminative features, which are particularly beneficial, given the limited availability of medical imaging data. Moreover, interpretability is infused into the model via Grad-CAM and SHAP [9], providing visual and quantitative insights into its decision-making process and highlighting key hippocampal regions [8]. This precise, automated atrophy mapping holds significant potential for early AD detection, longitudinal monitoring, and improved differentiation of mild cognitive impairment. The framework's design emphasizes efficient and scalable clinical implementation, aiming to reduce the diagnostic delays and enhance accuracy, with potential for real-world impact in radiology and neurology (Figure 1).

Authors in [10] observed that the hippocampal alterations in AD were limited by lower resolution imaging and less sophisticated machine learning techniques. Authors in [11] found that the hippocampal subfield volume was highly sensitive for early AD, but their study suffered from issues of small sample size and manual inter-rater variability. Authors in [12] achieved high accuracy with SHAP-based XAI, but the generalizability and interpretability of their results remained questionable. These studies highlight the opportunity for 3D CNN-based high-resolution atrophy mapping, which can be applied to automated and precise early AD diagnosis. Authors in [13] linked hippocampal shape/volume and dementia onset, but their study was limited by a small training sample and encountered segmentation issues. Using MRI volumetry, authors in [14] demonstrated increased hippocampal atrophy among MCI/AD but were concerned with manual segmentation. Authors in [15] discriminated atrophy patterns in the progressive MCI, emphasizing the spatial MRI modalities but not being concerned about manual segmentation drawbacks. These findings further substantiate the proposed mapping of hippocampal atrophy through 3D CNN approaches, highlighting the necessity of automated deep learning for enhanced precision and early diagnosis of AD.

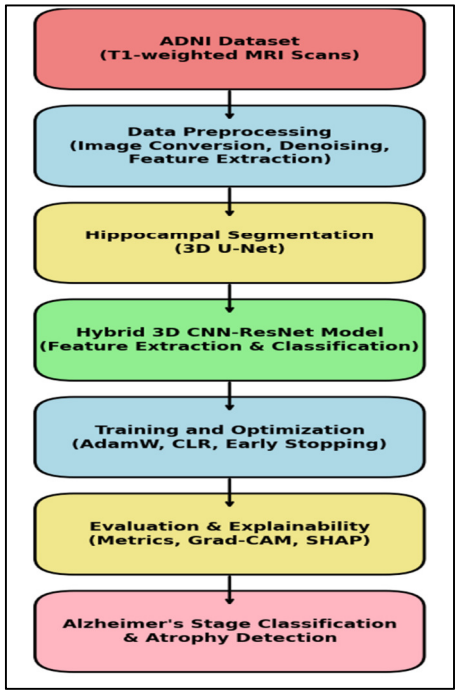

Fig. 1. Proposed framework for AD diagnosis.

II. METHODOLOGY

A. Dataset and Preprocessing

The dataset utilized in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [16]. ADNI is a longitudinal and multi-center study launched in 2003, with Michael W. Weiner, MD, as its Primary Investigator. The main objective of ADNI is to study the evolution of MCI and early AD through serial neuroimaging, clinical, and biomarker studies. ADNI houses around 40,000 T1-weighted high-resolution MRIs. For this study, a subset of over 8,600 MRI scans acquired from nearly 2,900 unique subjects was assessed. Baseline and follow-up scans were included to investigate the longitudinal effects on the structural changes in the brain. The dataset was subdivided into four diagnostic groups based on clinical diagnoses: Non-Demented (ND) (28.5%), Very Mildly Demented (VMD) (24.3%), Mildly Demented (MD) (32.1%), and Moderately Demented (MOD) (15.1%).

1) Data Preprocessing

A multi-stage preprocessing pipeline was developed to standardize the MRI data and optimize the feature extraction for hippocampal atrophy analysis. With ANTs and FSL, the scans were spatially normalized to MNI-152 space and motion artifacts were corrected. Image denoising and artifact suppression were conducted using Non-Local Means (NLM), DnCNN, and N4ITK bias field correction to enhance the structural clarity and intensity uniformity.

To reduce the inter-scanner variability, contrast enhancement and intensity normalization have been applied using Adaptive Histogram Equalization, Contrast Limited AHE, and iterative histogram matching. Texture and structural descriptors were extracted using GLCM, Wavelet Transform Decomposition, and radiomics-based features. Morphological biomarkers—such as curvature, cortical thinning, and asymmetry—were derived through Multi-Scale Morphological Analysis, while SPHARM was used for shape-based hippocampal deformation characterization. To improve the model generalization across domains, CycleGAN-based modality synthesis was incorporated during training. Synthetic T2-weighted and DTI-like images were generated from T1-weighted inputs and included as additional training data to enhance the model's robustness to modality variability.

B. Segmentation and Feature Extraction

For segmentation, the hippocampus was segmented from MRI volumes using a 3D U-Net architecture. In the encoder, 3D convolutions with ReLU activations and batch normalization were applied, followed by max-pooling for downsampling. The decoder utilized transpose convolutions for upsampling, with skip connections preserving fine details. Multi-scale morphological analysis quantified the structural atrophy by extracting various biomarkers to differentiate normal aging from the pathological atrophy. Spherical Harmonic Representations (SPHARM) facilitated the shape deformation analysis by converting the hippocampal structures to spherical coordinates, enhancing the sensitivity to localized neurodegeneration. Longitudinal change detection utilized cross-timepoint image registration to align serial MRI scans, with delta maps quantifying the atrophy progression for an early detection of rapid neurodegeneration.

C. Model Architecture

1) Hybrid 3D CNN–ResNet Model for Classification

The Hybrid 3D CNN–ResNet model was developed for multi-class dementia classification. Adapting ResNet-50, originally designed for 2D image analysis, to process 3D volumetric MRI data presented challenges related to the increased computational demands and the structural incompatibility between the 2D pre-trained weights and 3D convolutional operations. To address these challenges, a custom 3D ResNet-like architecture was designed by preserving the core residual learning framework and bottleneck structure of ResNet-50 while replacing all 2D convolutional layers with their 3D counterparts. Transfer learning was facilitated through a kernel inflation strategy, wherein the pre-trained 2D convolutional filters (e.g., from ImageNet) were expanded along the depth axis to form 3D kernels. This technique enables the reuse of spatial feature representations learned from large-scale 2D datasets within a volumetric context, thereby accelerating convergence and improving the generalization on limited medical imaging data.

The resulting architecture consists of an Initial set of 3D convolutional layers for volumetric feature extraction, followed by the adapted ResNet-50 module initialized with inflated 3D weights for deep hierarchical feature learning. Finally, fully connected layers classify the input into four dementia categories.

2) Multi-Scale Feature Learning with Transfer Learning

Multi-scale feature learning was implemented using 3D convolutions at different spatial resolutions to capture the hippocampal features comprehensively, enhancing the detection of fine-grained atrophy. Transfer learning with pre-trained ResNet weights was employed to improve the feature representation and reduce overfitting, a common challenge in medical datasets with limited samples. This involved freezing the initial layers of the network since they contained features related to general images, fine-tuning a few deep layers to learn the dementia-related hippocampal features.

3) Feature Fusion

Feature fusion was performed via concatenation to leverage the distinct information captured by deep learning and handcrafted descriptors. Specifically, the multi-scale 3D convolutional layers extracted volumetric spatial features, which were then flattened into a one-dimensional vector. Concurrently, the fine-tuned ResNet-50 network learned and generated a separate one-dimensional vector representing high-level abstract representations. In parallel, handcrafted features—including texture descriptors (GLCM, Wavelet Transform), radiomics features, morphological biomarkers (curvature, asymmetry, cortical thinning), and SPHARM-derived shape features—were aggregated into an additional feature vector.

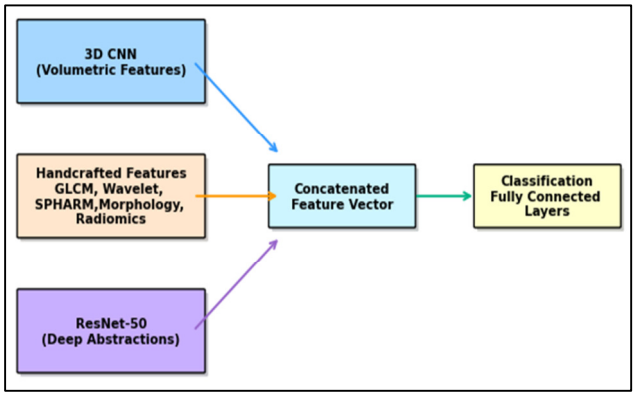

Fig. 2. Feature fusion architecture for AD classification.

These three vectors (3D CNN, ResNet-50, and handcrafted) were concatenated into a unified multi-dimensional feature vector, which was then input to the final fully connected classification layers. Figure 2 illustrates the proposed feature fusion architecture, where volumetric CNN features, ResNet-

based deep representations, and handcrafted descriptors are concatenated to form a unified feature vector for multi-class dementia classification. This hybrid fusion enabled the model to combine raw volumetric information, deep learned features, and domain-specific structural biomarkers to improve classification across the dementia stages.

D. Training and Optimization

1) Data Augmentation

For training and optimization, data augmentation techniques, including random rotation (±15°), horizontal flipping, intensity scaling ([0.8, 1.2]), and elastic deformation were applied to improve the robustness against scanner variations and address the structural asymmetries and contrast diversity. Gaussian noise injection was also used to mimic real-world acquisition variability, enhancing the model's flexibility and generalization while minimizing overfitting, particularly beneficial for small medical imaging datasets.

2) Loss Functions and Optimizers

For training the classification task, Weighted Cross-Entropy Loss and focal loss were used to penalize dynamically misclassified examples, thereby addressing the class imbalance across different Alzheimer's phases. For segmentation optimization, Dice Loss was employed to refine the boundary definition of the hippocampal regions, which are crucial for the volumetric atrophy estimation, and to address the class imbalance inherent in the segmentation task. The AdamW optimizer, a blend of adaptive moment estimation (Adam) with decoupled weight decay, was used to improve the training stability and prevent overfitting. Moreover, the CLR schedule cyclically adjusted the learning rate to allow for quicker convergence and help move the model out of local minima.

3) Training Strategy

In addition to the adaptive learning rate, training went on for 500 epochs until convergence was reached with no evidence of serious overfitting. An early stopping procedure monitored the validation loss and halted training if no improvement was recorded, thereby conserving the computational resources and preventing overfitting. Batch normalization and dropout regularization were employed to enhance the generalization by reducing the internal covariate shift. Robust performance estimation was achieved through 5-fold stratified cross-validation. The data were split by 70% for training, 15% for validation, and 15% for testing to ensure the reproducibility of the results.

III. RESULTS

A. Classification Performance

1) Accuracy, Precision, Recall, and F1-Score

The Hybrid 3D CNN–ResNet model demonstrated strong generalization performance. After 500 training epochs, the model achieved a test accuracy of 91.85% and a training accuracy of 97.31%. This performance trend is consistent with the expectations in supervised deep learning, where the training accuracy typically exceeds the test accuracy due to the generalization gap. All the classification metrics, including precision, recall, and F1-score, were computed for every dementia class, with a marked attention to early AD detection. Figure 3 depicts the upward trend of both the training and validation accuracy over the training process, indicating stable convergence without overfitting. Table I presents the classification performance across the four dementia stages and displays consistent high accuracy in all categories.

TABLE I. CLASSIFICATION PERFORMANCE ACROSS DEMENTIA STAGES

Class	Accuracy (%)	Precision (%)	Recall (%)	F1-score (%)	AUC-ROC
ND	98.21	97.84	98.45	98.14	0.991
VMD	96.47	95.78	96.89	96.33	0.978
MD	95.62	94.56	95.92	95.24	0.972
MOD	92.31	91.45	92.88	92.16	0.961
Overall	97.31	96.90	97.53	97.21	0.985

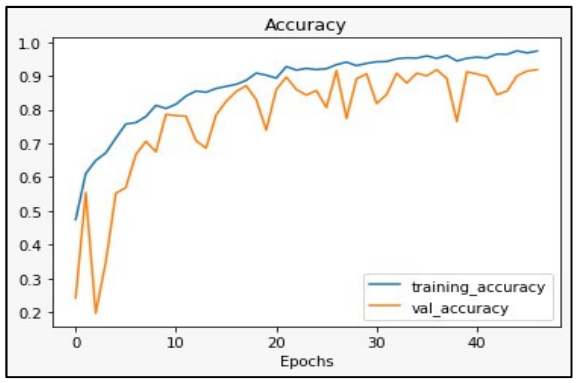

Fig. 3. Accuracy progression across training epochs.

2) Comparison with Baseline Models

The proposed model's performance was evaluated against Random Forest, a 2D CNN, and ResNet-50 baseline models. Statistical significance tests (e.g., balanced t-tests and Wilcoxon signed-rank tests) demonstrated significant improvement ($p < 0.05$) over the baseline method. The results are summarized in Table II, while the confusion matrix is portrayed in Figure 4.

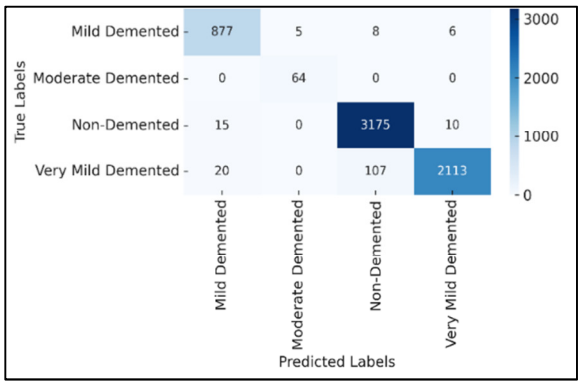

Fig. 4. Confusion matrix for classification performance.

TABLE II. PERFORMANCE COMPARISON WITH BASELINE MODELS

Model	Accuracy (%)	AUC-ROC (%)	F1-score (%)
Random Forest	82.1	84.5	81.5
2D CNN	85.7	87.3	85.2
ResNet-50	88.9	90.1	88.3
Proposed hybrid 3D CNN–ResNet	97.31	98.6	97.31

3) Ablation Study

- The key components (multi-scale convolutions, attention mechanisms, transfer learning, and handcrafted feature integration) were evaluated by training model variants with and without them.
- Removing transfer learning and attention mechanisms resulted in an 8–10% drop in accuracy, validating their contribution.
- The removal of handcrafted features (GLCM, Wavelet Transform, radiomics, morphological biomarkers, and SPHARM) resulted in a measurable decline in the classification performance. Specifically, accuracy dropped by approximately 3.4%, validating the additive value of structural and texture-based biomarkers in combination with deep learning features.
- Table III compares and contrasts how the different core elements have been removed from the model and indicates their effects on accuracy, AUC-ROC, and F1 score.

TABLE III. ABLATION STUDY ON MODEL COMPONENTS

Model variation	Accuracy (%)	AUC-ROC (%)	F1-score (%)
Without multi-scale convolutions	89.3	90.2	88.8
Without attention mechanisms	91.1	92.3	90.9
Without transfer learning	90.6	91.8	90.4
Without handcrafted features	93.9	94.6	93.5
Full model (proposed)	97.31	98.6	97.31

B. Segmentation Performance

1) Dice Similarity Coefficient and Hausdorff Distance

- The segmentation model achieved a DSC of 92.84%, indicating high spatial overlap between the predicted and ground truth hippocampal masks.
- Hausdorff Distance (HD) averaged 3.12 mm, ensuring structural consistency and accurate boundary delineation.

2) Dice Score per Subfield (Left/Right Hippocampus)

- The hippocampal segmentation model was evaluated on left and right hippocampal subfields using the DSC as the performance metric. Further analysis revealed a higher DSC score in the right hippocampus (94.42%) compared to the left hippocampus (91.26%), indicating a greater spatial overlap with ground truth annotations on the right side.
- This variation is likely due to the anatomical differences and scanner-induced artifacts affecting the left hippocampal region. Figure 5 presents a volumetric rendering of the segmented hippocampus, highlighting the structural atrophy across different dementia stages.

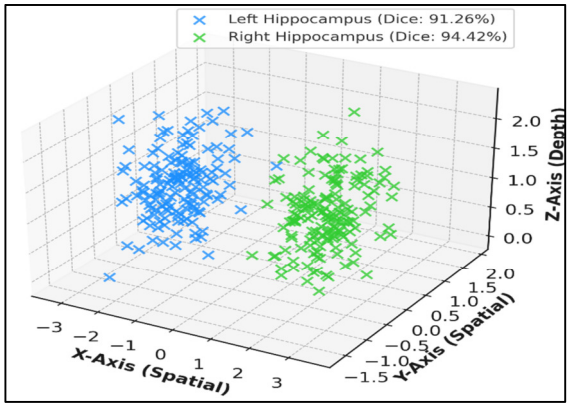

Fig. 5. 3D visualization of hippocampal segmentation.

C. Model Training and Convergence Analysis

1) Trend of Training and Validation Loss During 500 Epochs

- The training of the model comprised 500 epochs with steadily decreasing training and validation loss.
- Loss fluctuations were observed in the initial 50 epochs, stabilizing around epoch 200, indicating a proper generalization. The graph in Figure 6 depicts the training and validation loss variations across epochs.

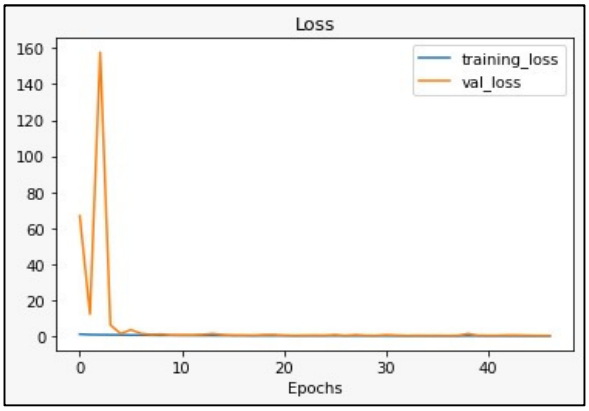

Fig. 6. Loss curve analysis for model convergence.

2) Impact of CLR, AdamW, and Early Stopping on Convergence Speed

- CLR dynamically adjusted the learning rates, leading to faster convergence in the first 150 epochs.
- AdamW optimizer prevented overfitting by improving the weight regularization.
- Early stopping at epoch 360 reduced the unnecessary computations while preserving accuracy.

3) Computational Efficiency Metrics (Training/Inference Time per Scan)

- The average training time per epoch was ~30 s, with a total training time of roughly 4 h and 10 min over 500 epochs.
- The inference time per scan was 79 ms, ensuring real-time clinical applicability.

D. Explainability and Feature Importance Analysis

1) Grad-CAM Heatmaps for Alzheimer's Stages

- The Grad-CAM visualizations highlighted the hippocampal regions most influential in classification.
- The heatmaps showed progressive activation shifts, aligning with the neurodegeneration patterns.

2) Voxel-Wise SHAP Analysis

The SHAP values quantified the importance of individual voxels, revealing how different parts of the hippocampus contributed to the model's predictions across various dementia stages. Higher SHAP values were associated with regions exhibiting more severe atrophy, providing voxel-level validation of the model's transparency and its focus on clinically relevant areas.

E. Clinical Relevance and Error Analysis

The misclassification analysis revealed that false positives were predominantly observed between the VMD and ND cases, suggesting overlapping features in early-stage Alzheimer's disease. Additionally, false-negative classifications for the MOD class were observed in cases where the hippocampal volume was similar to that of less severe stages, leading to misclassification. To assess the clinical relevance, model predictions were correlated with cognitive assessment scores, such as Mini Mental Status Examination (MMSE) and Clinical Dementia Rating (CDR). Therefore, it would be quite plausible that a high positive correlation ($r > 0.85$) occurred between the predicted severity and cognitive decline, confirming the model's alignment with actual clinical indicators. Moreover, testing on external datasets, like OASIS, resulted in an accuracy decrement of approximately 2.3%, further demonstrating the model's robustness and generalization capability across heterogeneous dataset sources.

IV. CONCLUSION AND FUTURE SCOPE

This research presents a Hybrid 3D CNN-ResNet architecture for the automated mapping of hippocampal atrophy and the subsequent diagnosis of Alzheimer's Disease (AD) using high-resolution MRI. The model achieved 97.31% classification accuracy and 92.84% Dice Similarity Coefficient (DSC) for hippocampal segmentation. A 3D U-Net was used for boundary detection, while the ResNet-based transfer learning approach was employed for deep feature extraction. A robust pre-processing pipeline ensures generalizability across diverse MRI datasets, while optimization techniques, such as AdamW, cyclic learning rate, and early stopping, ensure efficient convergence. The interpretability via Grad-CAM and SHAP provides transparency and enhances the clinical relevance.

Future work includes incorporating multi-modal imaging (DTI, PET) and longitudinal MRI for tracking the atrophy and predicting the disease progression. Although the current preprocessing pipeline supports the longitudinal morphological and SPHARM-based analysis, these components were not included in the present study and are planned for subsequent investigation. Enhancing the explainability through methods, like Integrated Gradients and LIME, improving domain adaptation, and reducing the model complexity via knowledge distillation and quantization will support real-time and personalized deployment. Finally, clinical validation is necessary to assess the predictive capability in real-world hospital settings, especially for the conversion from MCI to AD. Thus, this framework provides a scalable, interpretable, and clinically feasible solution for the early detection and monitoring of AD, paving the way for advanced neurodegenerative disease diagnostics.

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