

Article

A Comparative Analysis of Gradient-Based, Edge-Based, and Segmentation-Based Data Augmentation Methods for Early Diagnosis of Alzheimer's Disease Using Neuroimaging Modalities and Deep Learning

Muhammad Dawood ^{1,†}, Usman Rasheed ^{1,†}, Waqas Ahmad ¹, Ahsan Bin Tufail ^{1,*} and Afnan Albahli ^{2,*‡}
for the Alzheimer's Disease Neuroimaging Initiative

¹ Department of Computer Science, The University of Chenab, Gujrat 50700, Pakistan

² Department of Information Technology, College of Computer and Information Sciences, Princess Nourah Bint Abdulrahman University, P.O. Box 84428, Riyadh 11671, Saudi Arabia

* Correspondence: ahsan@cs.uchenab.edu.pk (A.B.T.); amalbahli@pnu.edu.sa (A.A.)

† These authors contributed equally to this work.

‡ Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that causes progressive damage to brain neurons, leading to declines in cognitive and behavioral abilities. This deterioration often results in changes in personality and increasing difficulty in thinking and memory over time. Although there is no cure, early detection is crucial as it allows for more effective management and care. Advances in deep learning have significantly improved the accuracy of brain scan analysis for diagnostic purposes. In this study, we utilized the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset consisting of subjects diagnosed with AD, Mild Cognitive Impairment (MCI), and Normal Control (NC). Each participant has either Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) neuroimaging data, ensuring representation across heterogeneous modalities. The research focuses on comparing gradient-based, edge-based, and segmentation-based data augmentation techniques for early AD detection using neuroimaging and deep learning approaches, particularly 3D Convolutional Neural Networks (3D CNNs). Various augmentation methods were applied, including directional gradient, azimuth gradient direction, numerical gradient, Sobel horizontal edge filter, superpixel oversegmentation, and Canny edge detection. These techniques are evaluated in both binary and multiclass classification tasks involving MRI and PET scans. The results indicate that optimal performance varied depending on the task and modality. For PET-based classification, directional gradient performed the best for AD vs. NC binary classification, achieving an accuracy of 87.24%, while Canny edge detection was most effective for AD vs. MCI binary classification and AD-MCI-NC multiclass classification tasks, achieving accuracies of 72.77% and 59.04%, respectively. For MCI vs. NC, the best result (accuracy = 64.32%) is achieved by combining azimuth gradient direction with Sobel filtering. In contrast, for the MRI-based AD vs. NC classification task, the highest performance is achieved without applying augmentation (balanced accuracy = 60.90%). This research

Academic Editors: Jie Yang and Alice Miller

Received: 10 June 2026

Revised: 21 July 2026

Accepted: 22 July 2026

Published: 23 July 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

confirms the efficacy of data augmentation methods in the early diagnosis of AD in clinical settings.

Keywords: data augmentation; deep learning; convolutional neural networks; Alzheimer's disease; magnetic resonance imaging; positron emission tomography

1. Introduction

Alzheimer's disease (AD) remains the most common cause of dementia, although a variety of factors can lead to dementia. AD causes brain shrinkage, tissue loss, and neuronal death for elderly populations of the world. This condition imposes heavy socioeconomic difficulties on individuals and their caregivers, with damaging impact on the overall healthcare system. AD symptoms typically begin in the region surrounding the hippocampus and the entorhinal cortex. There is a progressive spread of deterioration from the medial temporal lobe to the parietal lobe to the frontal lobe and, in time, to the occipital lobe [1].

Even though AD was first discovered over a century ago, it still does not have a definitive cure to date, though current medications are only able to relieve the symptoms for a short period of time. For the alleviation of patient pain, a timely diagnosis of AD is needed. In addition, it facilitates the implementation of cutting-edge therapeutic treatments [2].

The number of occurrences of AD will spike in the next few years, as predicted by researchers. The development of accurate and effective diagnostic methods is needed to support clinicians, researchers, and caregivers. Neuroimaging modalities have proven essential for providing critical information and are expected to become increasingly relevant for early AD diagnosis. Several imaging modalities were used to detect gray matter atrophy, including amyloid imaging, Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Diffusion Tensor Imaging (DTI). Volumetric reduction in white matter, amyloid deposition, and examination of white matter integrity, as well as identifying brain lesions associated with cognitive decline in AD. Multiple postmortem studies analyzing brain tissue have shown that clinical diagnoses of AD are often inaccurate. Therefore, these neuroimaging modalities are essential for improving AD diagnostic accuracy [3].

Both Machine Learning (ML) and Deep Learning (DL)—AI methodologies—have been shown to be effective in detecting AD through multidimensional neuroimaging data [4]. A DL technique provides a comprehensive end-to-end process to autonomously discern meaningful features from data. A type of deep learning architecture, Convolutional Neural Networks (CNNs), uses convolutional operations to identify pooling layers and spatial patterns to reduce parameter complexity while preserving principal components [5].

Data augmentation techniques increase dataset diversity by generating new samples from existing data through various transformations. These approaches enhance the generalization and robustness of DL models by mitigating data dependency issues [6–8]. Data augmentation has also improved the performance of vision transformers and deep transfer learning architectures by providing regularization, facilitating manifold learning, and promoting invariant representations [9].

Neurofibrillary tangles and amyloid plaques build up in the brain, causing neuronal death in AD. Numerous studies have investigated early AD diagnosis using neuroimaging modalities. As an example, Meshrif Alruily et al. [10] developed an architecture for

multiclass AD classification using MRI scans, combining InceptionResNetV2, MobileNet, and VGG16. Their transfer learning-based approach obtained 97.93% accuracy using InceptionResNetV2, MobileNet, and VGG16. With ALZENET, MD Asaduzzaman et al. [11] developed an ensembled CNN architecture with ResNet-50, InceptionV3, and VGG16 for multiclass classification of AD based on MRI scans and achieved 97.31% accuracy. A DL framework with an adaptive fusion layer was proposed by Ahmad Muhammad et al. [12] for classifying AD using MRI scans. Their method achieved 99.42% accuracy. Using FusionNet, which combines multimodal (CT, PET, and MRI) and longitudinal imaging data for multiclass classification of AD, Shakhnoza Muksimova et al. [13] in their multiclass classification method achieved 94% accuracy. Yuhan Li et al. [14] utilized MRI and single-nucleotide polymorphism (SNP) data to develop a CNN-based multimodal architecture that can identify AD and Normal Control (NC), along with progressive Mild Cognitive Impairment (pMCI) and static MCI (sMCI). On the AD-NC task, it achieved 93.04% accuracy, whereas on the pMCI-sMCI task, it achieved 76.67% accuracy. Jacqueline Chua et al. [15] proposed an ensemble architecture comprising VGG-11, Swin transformer, Extreme Gradient Boosting, and Naïve Bayes algorithms to detect AD and MCI using Optical Coherence Tomography (OCT), achieving an area under the curve of 0.91 for the Asian population and 0.84 for the White population. Juan Zhou et al. [16] proposed a DL architecture combining a 3D-CNN model with a video Swin transformer using MRI data, achieving 92.92% accuracy on the AD vs. NC binary classification task. Mousavi et al. [17] tried Xception, VGG19, VGG16, and InceptionResNetV2 models for multiclass classification of AD based on MRI scans. InceptionResNetV2 achieved 98.52% accuracy for the multiclass classification task. Md. Khabir Uddin Ahamed et al. [18] employed a modified EfficientNetV2B3 architecture with a hybrid filtering approach for multiclass classification of AD using MRI scans, achieving 99.45% accuracy. Saeka Rahman et al. [19] introduced the NeuroNet-AD model, which integrates MRI scans with clinical metadata, achieving 98.68% accuracy on multiclass (NC, MCI, AD) classification and 98.67% on binary (AD vs. NC) classification. The CNN-based model developed by Tuan Vo et al. [20] achieved an accuracy of 84.62% when applied to binary classification (AD, NC) using electroencephalography (EEG) data. Seyed Majid Razavi et al. [21] utilized a network analysis framework in resting-state EEG based on Laplacian Eigenmaps to uncover the disruptions associated with AD. Their results indicate a void of brain state transitions in AD subjects. Jia-Le Wang et al. [22] developed synthetic cholecystokinin B receptor (CCKBR) agonists, reducing amyloid-beta plaques in mice, suggesting that synthetic biased agonists have therapeutic potential for AD.

While existing literature highlights the utility of deep learning, it frequently overlooks the danger of applying arbitrary transformations universally across distinct imaging physics. The presented work addresses this critical gap by establishing that data augmentation is modality-dependent and mapping out task-specific augmentation responses in the 3D domain. Prior works generally implemented uniform augmentations across datasets regardless of whether they measured structural anatomy or functional metabolism. The presented study demonstrates that while PET-based frameworks experience pronounced accuracy gains when integrated with targeted augmentations, structural MRI-based workflows perform optimally without them. This reveals a critical methodological constraint: spatial or edge-based filters risk distorting vital anatomical landmarks such as cortical atrophy boundaries and hippocampal volume loss, ultimately degrading classification performance.

The primary need for this research is to enable accurate, early detection of AD using deep learning and neuroimaging, which is crucial since the disorder currently has no definitive cure. First, AD cases are projected to spike rapidly, imposing massive socioeconomic strains on families and healthcare systems. Secondly, postmortem studies reveal

frequent inaccuracies in routine clinical diagnoses, highlighting the critical need for precise neuroimaging analysis. Thirdly, DL models face data scarcity and overfitting risks, making effective data augmentation vital for robustness. Finally, applying arbitrary augmentations on structural modalities like MRI can inadvertently distort vital anatomical features like hippocampal volume loss. Figure 1 displays research needs and methodological challenges involved in the early diagnosis of AD.

This paper introduces a tailored, task-specific approach to data augmentation in the 3D domain. We demonstrate that data augmentation is not universally beneficial across all imaging modalities. While PET-based frameworks show significant accuracy gains when coupled with customized augmentations, MRI-based classification performs optimally without augmentation, revealing that structural transformations risk distorting crucial anatomical details like cortical atrophy. In addition to that, we provide a comprehensive evaluation of six distinct augmentation techniques—including directional, azimuth, and numerical gradients; the Sobel filter; the Canny edge detector; and superpixel oversegmentation. Instead of employing standard data augmentation methods such as flipping, cropping, translation, rotation, etc., we applied task- and modality-specific data augmentation methods tailored to the physics of PET and MRI neuroimaging modalities. This study also introduces anatomical distortion awareness, as we found that in MRI filtering, it distorts cortical landmarks in comparison to contemporary studies. Finally, in comparison to other studies, this study provides diagnostic granularity by studying three binary and one multiclass classification tasks.

This study compares gradient-based, edge-based, and segmentation-based data augmentation methods for early diagnosis of AD using MRI and PET neuroimaging modalities with DL techniques. For PET, the performance of directional gradient, azimuth gradient direction, numerical gradient, Sobel horizontal edge-emphasizing filter, superpixel oversegmentation, Canny edge detection, and their combinations as data augmentation methods in the 3D domain are evaluated using a CNN architecture. Three binary classification tasks (AD vs. NC, AD vs. MCI, MCI vs. NC) and one multiclass classification task (AD vs. MCI vs. NC) were investigated using PET data. For MRI, the study assessed the performance of directional gradient, azimuth gradient direction, numerical gradient, Sobel horizontal edge-emphasizing filter, and superpixel oversegmentation augmentation methods in the 3D domain using a CNN architecture. Only the AD vs. NC binary classification problem was examined using MRI data.

The core research questions that we studied are as follows:

- Which 3D augmentation strategy maximizes classification accuracy for 3D-CNN architectures?
- How does augmentation efficacy change when shifting from metabolic PET to structural MRI?
- What specific transformation combinations optimize detection of intermediate transitional clinical stages?
- Do edge-emphasizing filters distort vital cortical atrophy or hippocampal landmarks?

The structure of this article is systematically organized as follows: Section 2 describes the experiments using PET and MRI datasets. Section 3 explains the 3D-CNN architecture and data augmentation methods. In Section 4, we describe the experimental procedures, and in Section 5, we present the results. The paper's findings are discussed in Section 6, and the conclusions are presented in Section 7.

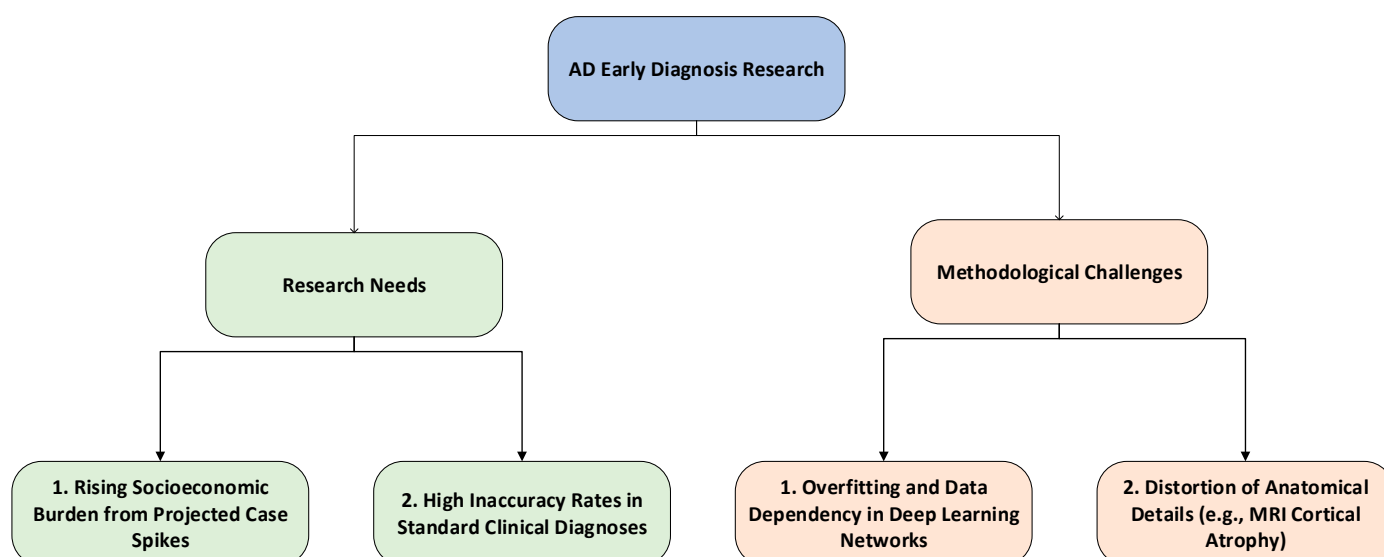


Figure 1. Structural tree diagram illustrating the clinical needs and methodological challenges of early AD diagnosis research. The green nodes represent the socioeconomic and diagnostic drivers necessitating the study, while the red nodes delineate the architectural and data-driven constraints encountered during deep learning model implementation.

2. Datasets Description

As a data source for these experiments, we used the PET dataset from the ADNI, a longitudinal study aimed at validating biomarker images for AD in a clinical scenario. Subject demographics, presented as mean (min–max), are provided in Table 1. The experiments employ ADNI 1 baseline, spatially normalized, and smoothed PET scans in the three-dimensional domain.

The MRI dataset used in these experiments is also obtained from ADNI. Subject demographics, reported as mean (min–max), are listed in Table 2. The experiments utilize post-processed tensor-based morphometry Jacobian maps in the 3D domain.

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI [23] was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The original goal of ADNI was to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The current goals include validating biomarkers for clinical trials, improving the generalizability of ADNI data by increasing diversity in the participant cohort, and providing data concerning the diagnosis and progression of Alzheimer’s disease to the scientific community. For up-to-date information, see adni.loni.usc.edu.

Table 1. Demographics of subjects with PET scans.

Research Group	AD	MCI	NC
Number of Subjects	94	97	102
Age	75.82 (55.3–88)	74.54 (55.3–87.2)	76.01 (62.2–86.6)
NPI-Q Score	4.074 (0–15)	1.97 (0–17)	0.402 (0–5)
FAQ Score	13.67 (0–27)	3.16 (0–15)	0.186 (0–6)

NPI-Q: Neuropsychiatric Inventory Questionnaire, FAQ: Functional Activities Questionnaire.

Table 2. Demographics of subjects with MRI scans.

Research Group	AD	NC
Number of Subjects	188	188
Age	75.36 (55–91)	76.7 (60–90)

3. Methodology

In this section, the study elaborates on the detailed methodology of our proposed approach in subsequent sections.

3.1. 3D-CNN Architectures Utilized in MRI and PET Studies

Figures 2 and 3 illustrate the deep learning-based 3D-CNN architectures employed in this study. As shown in Figure 2, 3D-CNN architectures were developed to classify subjects for binary (AD vs. MCI, MCI vs. NC, AD vs. NC) and multiclass classification tasks (AD vs. MCI vs. NC) using PET modality. Using the MRI neuroimaging modality, Figure 3 shows the 3D-CNN architecture for the AD vs. NC binary classification task. The input layer size for PET scans is $79 \times 95 \times 69$, while for MRI, it is $220 \times 220 \times 220$. Inputs are normalized by subtracting the mean to enhance training stability and accelerate convergence. Over the input layer, a convolutional layer is added with a kernel size of 3, which is used to extract features and form feature maps based on these features. To ensure that the output maintains the same dimensions as the input—zero padding is applied—the framework automatically calculates and adds the exact amount of zeros needed so that the output spatial dimensions match the input dimensions. To mitigate overfitting, to maintain small weights, and to improve generalization, L2 regularization is applied to biases and weights. Afterwards, the convolutional layer is followed by a batch normalization layer, which facilitates faster model training, reduces vanishing gradients, and acts as a stabilizing mechanism by regularizing the learning process. It is then followed by an Exponential Linear Unit (ELU) activation layer. By utilizing an alpha value of one, it provides the model with the ability to learn more complex patterns as a result. Following the ELU activation layer, the 3D Max pooling layer reduces the size of feature maps. It extracts dominant translation-invariant features and minimizes feature extraction computational costs by reducing the number of feature maps. The convolutional layer, the batch normalization layer, the ELU activation layer, and the Max pooling layer are all part of a block called Block A, which is repeated five times in a row. Block B is the next block in the architecture comprising 3 fully connected (FC) layers, a softmax layer, and a classification layer. In the FC layer, every input neuron is connected to every output neuron. In this way, the FC layer facilitates classification or feature combination by mapping features to probabilities and facilitating the process of final decision-making. The Softmax layer converts the FC layer's output values into class probabilities, selecting the most probable class. Finally, the classification layer receives the probabilities from the softmax layer, compares them with the true labels, computes the cross-entropy classification loss, and backpropagates this loss through the network during backpropagation.

In Figures 2 and 3, the parameters are set as follows: $n_1 = 100$, $n_2 = 30$, $n_3 = 2$, and the number of filters is 15 for all binary (AD vs. NC, AD vs. MCI, MCI vs. NC) classification tasks using both MRI and PET scans. For the AD vs. MCI vs. NC multiclass task using only PET scans, as shown in Figure 2, $n_1 = 100$, $n_2 = 30$, $n_3 = 3$, and the number of filters remains 15.

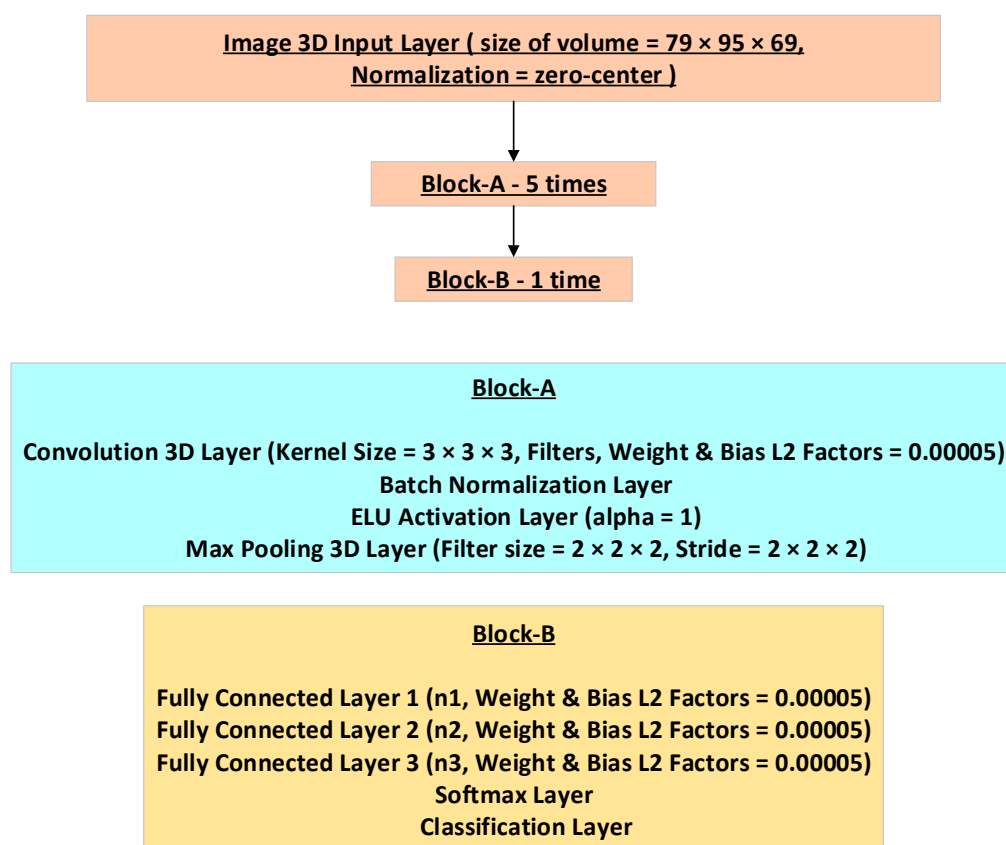


Figure 2. Based on the PET neuroimaging modality, a 3D-CNN architecture has been developed to perform binary and multiclass classification tasks.

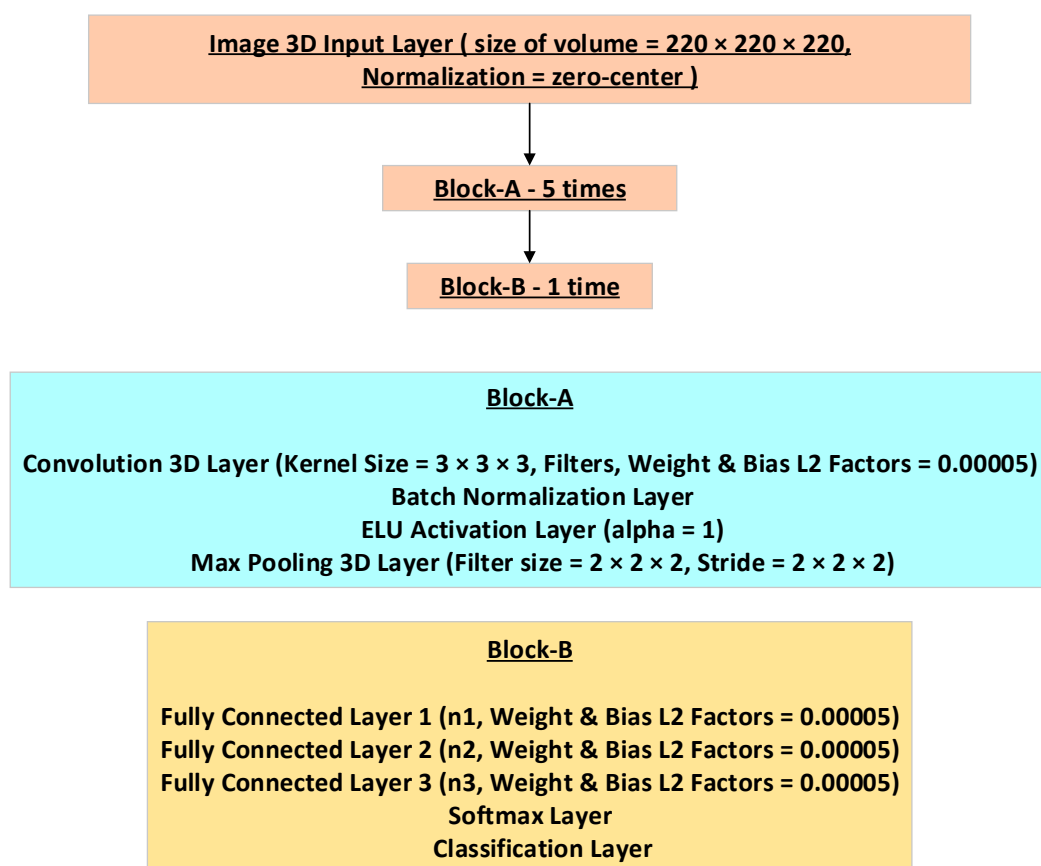


Figure 3. 3D-CNN architecture for the AD-NC binary classification task using the MRI neuroimaging modality.

Table 3 shows detailed architecture hyperparameters for 3D-CNN architectures that utilize PET scans, while Table 4 shows detailed architecture hyperparameters for 3D-CNN architectures that utilize MRI scans.

Table 3. Architecture hyperparameters for our proposed 3D-CNN model utilizing PET scans.

Layer	Filter Size	Number of Filters	Stride Size	Output Size
Conv1 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 79 \times 95 \times 69$
MaxPool1	$2 \times 2 \times 2$	-	2	$15 \times 40 \times 48 \times 35$
Conv2 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 40 \times 48 \times 35$
MaxPool2	$2 \times 2 \times 2$	-	2	$15 \times 20 \times 24 \times 18$
Conv3 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 20 \times 24 \times 18$
MaxPool3	$2 \times 2 \times 2$	-	2	$15 \times 10 \times 12 \times 9$
Conv4 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 10 \times 12 \times 9$
MaxPool4	$2 \times 2 \times 2$	-	2	$15 \times 5 \times 6 \times 5$
Conv5 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 5 \times 6 \times 5$
MaxPool5	$2 \times 2 \times 2$	-	2	$15 \times 3 \times 3 \times 3$
FC 1		100	-	100
FC 2		30	-	30
FC 3		2 or 3	-	2 (binary) or 3 (multiclass)
Softmax		-	-	2 (binary) or 3 (multiclass)

Table 4. Architecture hyperparameters for our proposed 3D-CNN model utilizing MRI scans.

Layer	Filter Size	Number of Filters	Stride Size	Output Size
Conv1 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 220 \times 220 \times 220$
MaxPool1	$2 \times 2 \times 2$	-	2	$15 \times 110 \times 110 \times 110$
Conv2 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 110 \times 110 \times 110$
MaxPool2	$2 \times 2 \times 2$	-	2	$15 \times 55 \times 55 \times 55$
Conv3 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 55 \times 55 \times 55$
MaxPool3	$2 \times 2 \times 2$	-	2	$15 \times 28 \times 28 \times 28$
Conv4 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 28 \times 28 \times 28$
MaxPool4	$2 \times 2 \times 2$	-	2	$15 \times 14 \times 14 \times 14$
Conv5 + BN + ELU	$3 \times 3 \times 3$	15	1	$15 \times 14 \times 14 \times 14$
MaxPool5	$2 \times 2 \times 2$	-	2	$15 \times 7 \times 7 \times 7$
FC 1		100	-	100
FC 2		30	-	30
FC 3		2	-	2
Softmax		-	-	2

3.2. Data Augmentation Methods

In this section, the study elaborates each of the selected data augmentation techniques in subsequent sections.

3.2.1. Directional Gradient

The directional derivative quantifies the rate of change in a function in a specified direction at a given point. It represents a special case of the Gateaux derivative. Partial derivatives can be generalized to determine the slope in any direction. Level curves are

consistently perpendicular to this gradient. This augmentation technique is implemented using the MATLAB (2025a) function `imgradientxyz`.

3.2.2. Azimuth Gradient Direction

When a gradient is non-zero at a given location, the gradient direction determines the direction in which the function increases most rapidly when the gradient is non-zero. Alternatively, it can be described as the direction of steepest descent for the cost function, pointing towards the feasible region. The objective function decreases at the highest local rate with any small movement in the direction of the negative gradient. This augmentation technique is implemented using the MATLAB function `imgradient3`.

3.2.3. Numerical Gradient

The numerical gradient estimates the values of the partial derivatives of the function in each dimension based on the known values of the function. The gradient can be conceptualized as a set of vectors pointing in the direction of increasing function values. This augmentation strategy is implemented using the MATLAB function `gradient`.

3.2.4. Sobel Horizontal Edge-Emphasizing Filter

This filter approximates the vertical gradient to emphasize horizontal edges. The gradient intensity is computed to enhance edge visibility. Additionally, this filter may blur distinctions between objects within the image. This augmentation approach is implemented using the MATLAB functions `fspecial` and `imfilter`.

3.2.5. Superpixel Oversegmentation

This procedure creates cluster centers and iteratively updates their coordinates as pixels are assigned to the nearest cluster center. We can identify the closest cluster center based on the spatial and intensity distances between pixels for each pixel. This is done using a distance metric that aggregates the distances between pixels. Low compactness values produce more irregularly shaped superpixels that better adhere to the boundaries, while higher values yield more uniformly shaped superpixels. This approach enables the consistent interpretation of compactness values across all images. This augmentation approach is implemented using the MATLAB function `superpixels3`.

3.2.6. Canny Edge Detection

This multi-stage approach applies Gaussian smoothing to reduce noise, computes gradients to measure intensity changes, and uses non-maximum suppression and hysteresis thresholding to connect appropriately selected edges. This augmentation approach is implemented using the MATLAB function `edge3`.

Table 5 shows the parameters of data augmentation schemes using both MRI and PET scans that are considered in this study, while Table 6 presents a methodological comparison of the implemented 3D data augmentation techniques.

Table 5. Parameters of data augmentation schemes considered in this study.

Augmentation Scheme	Parameters	MATLAB Function
Directional Gradient	For both MRI and PET scans: returns directional gradients using the Sobel gradient operator. The gradient of a pixel is a weighted sum of pixels.	<code>imgradientxyz</code>

Azimuth Gradient Direction	For both MRI and PET scans: returns gradient direction using the Sobel gradient operator.	imgradient3
Numerical Gradient	For both MRI and PET scans: estimate the value of the partial derivative in each dimension. The result corresponds to the horizontal difference.	gradient
Sobel Horizontal Edge-Emphasizing Filter	For both MRI and PET scans: returns a 3×3 filter that emphasizes horizontal edges with a smoothing effect that approximates a vertical gradient.	fspecial, imfilter
Superpixel Oversegmentation	Number of superpixels = 650 (MRI), 700 (PET).	superpixels3
Canny Edge Detection	For PET scans only: “approxcanny”, thresh = 10^{-2} , sigma = 10^{-5}	edge3

Table 6. Methodological comparison of the implemented 3D data augmentation techniques.

Augmentation Scheme	Framework	Focus	Main Advantage
Directional Gradient	First-order partial derivatives	Captures spatial intensity changes	Able to discriminate between edges and boundaries based on spatial profile
Azimuth Gradient Direction	Direction of steepest descent	Direction of negative gradient	Captures directional shifts in PET/MRI scans
Numerical Gradient	Second order difference approximation	Direction of increasing function values	Provides structural smoothing
Sobel Horizontal Edge Emphasizing Filter	Vertical gradient approximation	Computation of gradient intensity	Enhances edge visibility by introducing blurring within the image
Superpixel Oversegmentation	Creates cluster centers based on spatial and intensity distances	Aggregation of distances between pixels	Ensure compactness across all images
Canny Edge Detection	Multistage approach	(1) Application of Gaussian smoothing, (2) Computation of gradients to measure intensity changes, (3) non-maximum suppression, (4) Hysteresis thresholding	It can capture weak pathways in PET brain scans

4. Experiments

A five-fold cross-validation approach is implemented for experiments utilizing PET scans. This paper addresses three binary classification tasks (AD vs. NC, MCI vs. NC, and AD vs. MCI) as well as one multiclass classification task (AD vs. MCI vs. NC). Zero-centered normalization is applied in the input layer to standardize the data to get a mean of 0 and a standard deviation of 1 at the end of the layer. The Adam optimization algorithm is used in all experiments. A mini-batch size of 2 is selected. In this model, the initial learning rate (lr) and number of epochs are set to 0.001 and 50, respectively. After every 10 training epochs, 0.1 is multiplied by the current value of lr, following a piecewise lr reduction schedule. The training data is shuffled randomly after each epoch.

A six-fold cross-validation approach is implemented for experiments utilizing MRI scans, focusing on the AD vs. NC binary classification task. Zero-centered normalization is applied in the input layer to standardize the data to a mean of 0 and a standard deviation of 1. The Adam optimization algorithm is used for all experiments. Two mini-batches are selected. Initially, the hyperparameter tuning is done by setting lr to 0.001, the maxi-

imum number of epochs is set to 3, the lr drop period is 1, the lr is reduced by a factor of 10, and training data is randomly shuffled after each epoch. A piecewise lr reduction schedule is followed to reduce lr.

We applied augmentation to training set samples only to help the model learn generalizable patterns and prevent overfitting. By exposing the model to varied, artificial examples during training, it learns to ignore irrelevant details and performs better on unseen data. In addition, we split the datasets at the subject level for the experiments.

Generally speaking, training ends when it hits convergence, which indicates that no more weight changes take place and the training accuracy reaches its maximum. Now that the network has been trained, it functions as a generic feature extractor, much like a conventional feature-generating algorithm. Discriminative characteristics that are used to differentiate the classes are the generated features [24].

Total cumulative convolutional floating point operations per second (FLOPs) using PET modality data is around 1.36 billion FLOPs (1.36 GFLOPs), while that using MRI modality data is around 27.12 billion FLOPs (27.12 GFLOPs).

The time complexity of this 3D-CNN architecture is primarily driven by its convolutional layers, scaling linearly with the output feature map volume. This structural reality explains why the MRI processing loop runs significantly slower than the PET workflow, as the higher input resolution increases the total floating-point calculation pass count.

The time complexity for the 5-block 3D convolutional layer pipeline scales as

$$O\left(\sum_{l=1}^5 N_l K_d K_h K_w C_{l-1} C_l\right)$$

where N_l : Total number of voxels in the output feature map of block l ,

$K_d \times K_h \times K_w$: 3D kernel size set to $3 \times 3 \times 3$,

C_l : No. of filters per layer, fixed at 15 for all tasks.

Data augmentation schemes add deterministic, non-trainable time overheads during the training phase. For instance, the following apply:

- Gradient-based (Sobel/Numerical): $O(D \times H \times W)$ linear grid parsing.
- Canny Edge Detection: $O(D \times H \times W \log(D \times H \times W))$ due to multi-stage filtering and suppression.
- Superpixel Oversegmentation: $O(I \times K \times N)$ where 'I' is clustering iterations, 'K' is the no. of superpixels, and 'N' is voxel count.

In general, our 3D-CNN architectures achieved convergence. The training profiles for experiments involving PET scans have more fluctuations in comparison to those involving MRI scans. We observed loss curves to be smoother than accuracy curves for experiments involving both MRI and PET scans.

5. Results

All binary and multiclass classification tasks were evaluated in this study, and the results are presented in Tables 7–12. We evaluated the accuracy of binary classification tasks (AD-NC, AD-MCI, MCI-NC) using PET scans using sensitivity (SEN), specificity (SPEC), F-measure, precision, and balanced accuracy (BA) to assess the performance of binary classification tasks using PET scans. For the AD-MCI-NC multiclass classification task with PET scans, class-wise and macro-averaged SEN, SPEC, F-measure, precision, and BA are used. Accuracy, SEN, SPEC, F-measure, precision, and BA of the AD-NC binary classification task with MRI scans are evaluated to determine the performance of this task.

We have also provided performance metrics such as accuracy, Matthews' correlation coefficient (MCC), confusion matrices, geometric mean, and Cohen's kappa in the Supple-

mentary Materials. Figure 4 shows sample confusion matrices for both binary and multiclass classification tasks.

Based on PET scans, Table 7 presents the results for the AD-NC binary classification task. Results for the AD-MCI binary classification task are summarized in Table 8, while the results for the MCI-NC binary classification task are summarized in Table 9. In Tables 10 and 11, we reported the results for the AD vs. MCI vs. NC multiclass classification task with PET scans, using class-wise and macro-averaged performance metrics [6]. We can define the performance metrics for binary classification tasks as given in Equations (1)–(6). True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) are variables in Equations (1)–(6).

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN} \quad (1)$$

$$\text{SEN} = \frac{TP}{TP+FN} \quad (2)$$

$$\text{SPEC} = \frac{TN}{TN+FP} \quad (3)$$

$$\text{F-measure} = \frac{2TP}{2TP+FP+FN} \quad (4)$$

$$\text{Precision} = \frac{TP}{TP+FP} \quad (5)$$

$$\text{BA} = \frac{\text{SEN}+\text{SPEC}}{2} \quad (6)$$

Table 12 displays the results for the AD-NC binary classification task using MRI scans.

Table 7. Results of the AD-NC binary classification task using PET scans.

Augmentation Method	SEN	SPEC	F-Measure	Precision	BA
Directional Gradient	0.8404	0.9020	0.8634	0.8876	0.8712
Azimuth Gradient Direction	0.8191	0.8627	0.8324	0.8462	0.8409
Numerical Gradient	0.8511	0.8235	0.8333	0.8163	0.8373
Sobel Horizontal Edge-Emphasizing Filter	0.8511	0.8235	0.8333	0.8163	0.8373
Superpixel Oversegmentation	0.9149	0.2549	0.6719	0.5309	0.5849
Canny Edge Detection	0.8511	0.8235	0.8333	0.8163	0.8373
No Augmentation	0.8404	0.8431	0.8360	0.8316	0.8418
Directional Gradient +	0.8191	0.9118	0.8556	0.8953	0.8655
Azimuth Gradient Direction					

Table 8. Results of the AD-MCI binary classification task using PET scans.

Augmentation Method	SEN	SPEC	F-Measure	Precision	BA
Directional Gradient	0.7128	0.7320	0.7166	0.7204	0.7224
Azimuth Gradient Direction	0.6596	0.7216	0.6776	0.6966	0.6906
Numerical Gradient	0.7021	0.7320	0.7097	0.7174	0.7170
Sobel Horizontal Edge-Emphasizing Filter	0.6915	0.6804	0.6842	0.6771	0.6860
Superpixel Oversegmentation	0.7128	0.3505	0.5982	0.5154	0.5316
Canny Edge Detection	0.7766	0.6804	0.7374	0.7019	0.7285
No Augmentation	0.6702	0.7113	0.6811	0.6923	0.6908
Directional Gradient +					
Numerical Gradient	0.6809	0.6598	0.6702	0.6598	0.6703
Gradient					

Table 9. Results for the MCI-NC binary classification task using PET scans.

Augmentation Method	SEN	SPEC	F-Measure	Precision	BA
Directional Gradient	0.7216	0.4706	0.6335	0.5645	0.5961
Azimuth Gradient Direction	0.6082	0.6275	0.6082	0.6082	0.6178
Numerical Gradient	0.5979	0.5686	0.5829	0.5686	0.5833
Sobel Horizontal Edge-Emphasizing Filter	0.6804	0.5294	0.6256	0.5789	0.6049
Supapixel Oversegmentation	0.5567	0.4706	0.5268	0.5000	0.5136
Canny Edge Detection	0.567	0.6176	0.5759	0.5851	0.5923
No Augmentation	0.5670	0.6569	0.5882	0.6111	0.6119
Azimuth Gradient Direction + Sobel Horizontal Edge-Emphasizing Filter	0.5979	0.6863	0.6203	0.6444	0.6421

Table 10. Results for the AD-MCI-NC multiclass classification task using PET scans.

Augmentation Method	SEN	SPEC	F-Measure	Precision	BA
Directional Gradient	A: 0.7447,	A: 0.8141,	A: 0.6965,	A: 0.6542,	A: 0.7794,
	M: 0.3402,	M: 0.7755 ,	M: 0.3793,	M: 0.4286,	M: 0.5579,
	N: 0.6765	N: 0.7906	N: 0.6540	N: 0.6330	N: 0.7335
Azimuth Gradient Direction	A: 0.6702,	A: 0.8543 ,	A: 0.6774,	A: 0.6848,	A: 0.7622,
	M: 0.3608,	M: 0.6837,	M: 0.3608,	M: 0.3608,	M: 0.5222,
	N: 0.6078	N: 0.7801	N: 0.6019	N: 0.5962	N: 0.6940
Numerical Gradient	A: 0.7021,	A: 0.8241,	A: 0.6769,	A: 0.6535,	A: 0.7631,
	M: 0.4124,	M: 0.7245,	M: 0.4188,	M: 0.4255,	M: 0.5684,
	N: 0.6275	N: 0.8220	N: 0.6400	N: 0.6531	N: 0.7247
Sobel Horizontal Edge-Emphasizing Filter	A: 0.6809,	A: 0.8090,	A: 0.6531,	A: 0.6275,	A: 0.7449,
	M: 0.3918,	M: 0.7551,	M: 0.4153,	M: 0.4419 ,	M: 0.5734,
	N: 0.6765	N: 0.8115	N: 0.6667	N: 0.6571	N: 0.7440
Supapixel Oversegmentation	A: 0.6596,	A: 0.3819,	A: 0.4444,	A: 0.3351,	A: 0.5207,
	M: 0.3711,	M: 0.6837,	M: 0.3692,	M: 0.3673,	M: 0.5274,
	N: 0.0392	N: 0.9686	N: 0.0714	N: 0.4000	N: 0.5039
Canny Edge Detection	A: 0.7553 ,	A: 0.8392,	A: 0.7208 ,	A: 0.6893 ,	A: 0.7973 ,
	M: 0.4433 ,	M: 0.7041,	M: 0.4343 ,	M: 0.4257,	M: 0.5737 ,
	N: 0.5784	N: 0.8429	N: 0.6178	N: 0.6629	N: 0.7107
No Augmentation	A: 0.7021,	A: 0.8291,	A: 0.6804,	A: 0.6600,	A: 0.7656,
	M: 0.3299,	M: 0.7347,	M: 0.3536,	M: 0.3810,	M: 0.5323,
	N: 0.6471	N: 0.7749	N: 0.6256	N: 0.6055	N: 0.7110
Directional Gradient + Sobel Horizontal Edge-Emphasizing Filter	A: 0.6596,	A: 0.8141,	A: 0.6425,	A: 0.6263,	A: 0.7368,
	M: 0.3711,	M: 0.7194,	M: 0.3830,	M: 0.3956,	M: 0.5453,
	N: 0.6275	N: 0.7958	N: 0.6244	N: 0.6214	N: 0.7116

Note: AD = A; MCI = M; NC = N.

Table 11. Macro-averaged performance metrics for the AD-MCI-NC multiclass classification task using PET scans.

Augmentation Method	Macro-SEN	Macro-SPEC	Macro-F-Measure	Macro-Precision	Macro-BA
Directional Gradient	0.5871	0.7934	0.5766	0.5719	0.6903
Azimuth Gradient Direction	0.5463	0.7727	0.5467	0.5473	0.6595
Numerical Gradient	0.5807	0.7902	0.5786	0.5774	0.6854
Sobel Horizontal Edge-Emphasizing Filter	0.5831	0.7919	0.5784	0.5755	0.6874
Supapixel Oversegmentation	0.3566	0.6781	0.2950	0.3675	0.5173
Canny Edge Detection	0.5923	0.7954	0.5910	0.5926	0.6939
No Augmentation	0.5597	0.7796	0.5532	0.5488	0.6696
Directional Gradient + Sobel Horizontal Edge-Emphasizing Filter	0.5527	0.7764	0.5500	0.5478	0.6646

Table 12. Results for the AD-NC binary classification task using MRI scans.

Augmentation Method	Accuracy	SEN	SPEC	Precision	F-Measure	BA
Directional Gradient	0.5558	0.3564	0.7553	0.5929	0.4452	0.5558
Azimuth Gradient Direction	0.5399	0.7606	0.3191	0.5277	0.6231	0.5399
Numerical Gradient	0.5319	0.4309	0.6329	0.5400	0.4793	0.5319
Sobel Horizontal Edge-Emphasizing Filter	0.5053	0.6010	0.4096	0.5045	0.5485	0.5053
Supersixel Oversegmentation	0.5665	0.8032	0.3298	0.5451	0.6495	0.5665
No Augmentation	0.6090	0.5957	0.6223	0.6120	0.6038	0.6090

PREDICTED →

		AD	NC
ACTUAL ↓	AD	112	76
	NC	71	117

(a)

PREDICTED →

		AD	NC
ACTUAL ↓	AD	79	15
	NC	10	92

(b)

ACTUAL

↓

		PREDICTED →	
		AD	MCI
AD		62	32
MCI		27	70

(c)

ACTUAL

↓

		PREDICTED →	
		MCI	NC
MCI		59	38
NC		38	64

(d)

ACTUAL

↓

		PREDICTED →		
		AD	MCI	NC
AD		63	26	5
MCI		25	35	37
NC		4	36	62

(e)

Figure 4. Confusion matrices for the study: (a) AD-NC binary classification without augmentation using MRI modality, (b) AD-NC binary classification with directional gradient augmentation using PET modality, (c) AD-MCI binary classification with azimuth gradient direction augmentation using PET modality, (d) MCI-NC binary classification with azimuth gradient direction augmentation using PET modality, (e) AD-MCI-NC multiclass classification with azimuth gradient direction augmentation using PET modality.

6. Discussion

Based on PET scans, directional gradient augmentation provided the best performance for AD-NC binary classification. For the AD-MCI binary classification task using PET scans, the Canny edge detection data augmentation method produced the best result. A combination of azimuth gradient direction and Sobel horizontal edge-emphasizing filter augmentation methods achieved the best results for the MCI-NC binary classification task using the PET modality. For the AD-MCI-NC multiclass classification task using PET scans, the Canny edge detection data augmentation method yielded the best results. By contrast, the best results were obtained without augmentation when using MRI scans for the AD-NC binary classification task.

The experimental results demonstrate the effectiveness of data augmentation methods for PET based tasks. For instance, for AD-NC binary classification, the directional gradient augmentation yielded superior performance, which could be attributed to its ability to capture spatial intensity changes using first-order gradients leading to discrimination between edges and boundaries. For the AD-MCI and multiclass AD-MCI-NC PET based classification tasks, Canny edge detection yielded the best results. This could be due to incorporation of a multi-stage approach emphasizing on Gaussian smoothing, gradients computation, non-maximum suppression and hysteresis thresholding to capture weak pathways in brain PET scans on continuum between NC and AD of which MCI is an intermediate stage. For the MCI-NC PET modality based binary classification task, combining azimuth gradient direction with Sobel horizontal edge-emphasizing filtering proved most effective. This could be due to the fact that Sobel filtering enhances edge visibility through computation of gradient intensity while azimuth gradient direction technique effectively captures directional shifts in the direction of negative gradient. In contrast, for the AD-NC MRI based classification task, optimal performance was achieved without data augmentation. This could be due to the fact that the underlying structural changes in brain are distorted by augmentation based methods leading to a reduction in classification accuracy. PET modality outperforms MRI in detecting AD-related changes. This advantage arises because PET measures functional changes in the brain, while MRI assesses structural changes. AD is characterized by reduced metabolic activity in/around the temporal-parietal cortex, posterior cingulate cortex, and precuneus of the affected individual [25–33]. Reduced neuroplasticity is another hallmark of AD and is associated with a void of brain state transitions among AD subjects [21]. Lack of interregional communications in AD subjects could be compensated by increased use of default mode network by computing maximum flow pathways using a graph-theoretic approach leading to better care solutions for AD subjects [34].

Our proposed approach yielded promising results regarding the application of data augmentation methods and their combinations for the early diagnosis of AD. However, several limitations must be addressed in future studies to facilitate clinical translation. First, the sample size should be increased to fully leverage the capabilities of DL methods. Second, this study only used the ADNI dataset; future research should consider other datasets, such as the Open Access Series of Imaging Studies (OASIS) and the Australian Imaging Biomarkers and Lifestyle Study of Aging (AIBL). Third, explainable artificial intelligence techniques were not explored in this work. These methods can provide visual ex-

planations for decisions made by DL models, thereby helping users build appropriate trust in deep network predictions [35,36].

Practically, this modality-dependent framework can be integrated into clinical radiology workflows as an automated decision support tool that routes brain scans dynamically, using non-augmented 3D-CNNs for structural MRIs to avoid masking cortical atrophy boundaries and applying specialized gradient filters to PET scans to maximize early diagnostic accuracy. In pharmaceutical settings, this precise multi-class classification enables better patient stratification for clinical trials, allowing researchers to isolate transitional MCI stages and objectively track the efficacy of novel neuroprotective therapies against hippocampal or metabolic decline. Ultimately, deploying these standardized, physics-aware preprocessing pipelines helps smaller clinics overcome data scarcity, democratizes high-accuracy screening in underserved areas, and facilitates early care planning to alleviate massive socioeconomic burdens on families and healthcare systems.

To systematically evaluate the impact of the proposed 3D data augmentation strategies, we conducted an ablation study by comparing the top-performing specialized pipelines against baseline models trained completely without data augmentation (the ablated state). This analysis isolates the exact performance gains or drops attributable exclusively to the integration of modality-specific spatial transformations.

For metabolic PET neuroimaging tasks, removing the data augmentation component resulted in a consistent decline across all classification paradigms. In the AD vs. NC binary classification task, ablating the directional gradient filter reduced the balanced accuracy from 87.12% down to the baseline performance of 84.18%. Similarly, for the more challenging intermediate AD vs. MCI task, removing Canny edge detection degraded balanced accuracy from 72.85% to 69.08%. In the transitional MCI vs. NC stage, the removal of the joint azimuth gradient and Sobel horizontal filtering block caused a performance drop from 64.21% to 61.19% balanced accuracy. Finally, in the multi-class AD-MCI-NC scenario, ablating Canny edge detection lowered the macro-balanced accuracy from 69.39% to 66.96%. These results confirm that metabolic boundaries in PET scans are significantly enhanced by targeted edge and gradient operations, which mitigate data scarcity and improve feature representation.

Conversely, the ablation study revealed an entirely opposite paradigm for structural MRI neuroimaging. The baseline model operating without any data augmentation achieved the peak balanced accuracy of 60.90% for the MRI-based AD vs. NC classification task. Introducing any form of 3D spatial augmentation acted as a disruptive component rather than an enhancement. For instance, adding directional gradient operations dropped the accuracy to 55.58%, while superpixel oversegmentation and Sobel horizontal filtering degraded performance to 56.65% and 50.53%, respectively. This indicates that for high-resolution structural scans, edge-emphasizing or segmentation-based transformations distort critical, fine-grained anatomical landmarks like cortical boundaries and hippocampal volume profiles, confirming that the unaugmented baseline configuration remains optimal for structural workflows.

Tables 13 and 14 compare the proposed methods with existing techniques reported in the literature. The results indicate that our methods outperform other approaches across various classification scenarios, achieving superior outcomes for AD-NC, AD-MCI, MCI-NC, and AD-MCI-NC classification tasks.

Table 13. Comparison with other methods using the PET modality.

Reference	Modality	Method(s)	Accuracy	Classification Task
Our approach	PET	3D-CNN directional gradient	87.24%	AD-NC
Ahsan et al. [37]	PET	3D-CNN (Scenario-2)	86.22%	AD-NC
Ahsan et al. [38]	PET	3D-CNN Box Filtering augmentation	86.22%	AD-NC
Our approach	PET	3D-CNN Canny edge detection augmentation	72.77%	AD-MCI
Ahsan et al. [37]	PET	3D-CNN (Scenario-2)	69.1%	AD-MCI
Muhammad Athar et al. [6]	PET	3D-CNN Prewitt edge-emphasizing augmentation	70.68%	AD-MCI
Our approach	PET	3D-CNN Azimuth gradient direction + Sobel horizontal edge-emphasizing filter augmentations	64.32%	MCI-NC
Ahsan et al. [39]	PET	3D-CNN	62.25%	MCI-NC
Our approach	PET	3D-CNN Canny edge detection augmentation	59.04%	AD-MCI-NC
Ahsan et al. [37]	PET	3D-CNN (Scenario-2)	56.31%	AD-MCI-NC
Ahsan et al. [38]	PET	3D-CNN Gaussian filtering augmentation	55.63%	AD-MCI-NC
Muhammad Athar et al. [6]	PET	3D-CNN Prewitt edge-emphasizing augmentation	57.68%	AD-MCI-NC

Table 14. Comparison with other methods using MRI modality.

Reference	Data	Method	Performance Metrics	Classification Task
Our approach	MRI	3D-CNN (no augmentation)	SEN = 59.57% , SPEC = 62.23%, F-measure = 60.38% , Precision = 61.20% , Balanced Accuracy = 60.90% Accuracy = 60.9%	AD-NC
Ahsan et al. [39]	PET	2D-CNN	SEN = 42.88%, SPEC = 67.82% , F-measure = 48.23%, Precision = 55.11%, Balanced Accuracy = 55.35%	AD-NC

7. Conclusions

This study presents a comparative analysis of gradient-based, edge-based, and segmentation-based data augmentation methods for early diagnosis of AD using 3D-CNN architectures. For PET imaging, directional gradient achieved the highest AD-NC classification accuracy (87.24%), while Canny edge detection performed best for AD-MCI (accuracy = 72.77%) and AD-MCI-NC multiclass classification (accuracy = 59.04%) tasks. For MCI-NC classification, the best result (accuracy = 64.32%) is achieved by combining azimuth gradient direction with the Sobel filtering method. Notably, PET-based models benefited from augmentation, whereas MRI-based AD-NC classification performed best without it (balanced accuracy = 60.90%). The proposed models surpassed several state-of-the-art techniques across AD-NC, AD-MCI, and AD-MCI-NC multiclass classification tasks, highlighting the importance of tailored data augmentation in neuroimaging DL workflows. The results obtained in this study are promising; however, future work should expand the size and diversity of the dataset by including data sources such as OASIS and AIBL. The integration of explainable AI techniques will also be critical for providing “visual explanations” for model decisions, enhancing clinical trust, and assisting in the adoption of explainable AI in medical practice. In addition, integration of deeper learning models like 3D-ResNets in the proposed pipeline could potentially improve the performance further.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/sym18081254/s1>.

Author Contributions: Conceptualization, A.A., W.A., A.B.T., U.R. and M.D.; methodology, A.A., A.B.T., M.D., U.R. and W.A.; software, W.A., A.B.T., A.A., U.R. and M.D.; validation, W.A., U.R., M.D. and A.B.T.; formal analysis, A.B.T. and W.A.; investigation, A.A., W.A., U.R., M.D. and A.B.T.; resources, A.A. and A.B.T.; data curation, A.B.T. and W.A.; writing—original draft preparation, A.B.T., A.A., M.D., U.R. and W.A.; writing—review and editing, A.B.T., A.A., U.R., M.D. and W.A.; visualization, A.B.T. and W.A.; supervision, A.A., A.B.T. and W.A.; project administration, A.B.T., A.A. and W.A.; funding acquisition, A.B.T. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2026R970), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Data Availability Statement: The datasets employed for experiments in this study are publicly available at the ADNI website. The custom code developed for this study is available from the corresponding authors upon reasonable request.

Acknowledgments: The authors wish to express their sincerest gratitude to Indo Intan from Dipa Makassar University and Andrea Stevens Karnyoto from Bina Nusantara University for their valuable support, insights, and contributions to this research. Data collection and sharing for the Alzheimer’s Disease Neuroimaging Initiative (ADNI) is funded by the National Institute on Aging (National Institutes of Health Grant U19AG024904). The grantee organization is the Northern California Institute for Research and Education. In the past, ADNI has also received funding from the National Institute of Biomedical Imaging and Bioengineering, the Canadian Institutes of Health Research, and private sector contributions through the Foundation for the National Institutes of Health (FNIH), including generous contributions from the following: AbbVie; Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; BristolMyers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann–La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Naik, D.R.; Savyanavar, A. Comparative Analysis of Deep Learning Techniques in Alzheimer’s Disease Diagnosis: Trends, Challenges, and Future Directions. *MethodsX* **2026**, *16*, 103844. <https://doi.org/10.1016/j.mex.2026.103844>.
2. Hariharan, J.; Jothi, R. Alzheimer’s disease prediction using deep learning and XAI based interpretable feature selection from blood gene expression data. *Sci. Rep.* **2026**, *16*, 8022. <https://doi.org/10.1038/s41598-026-35260-8>.
3. Kobuti Ferreira, L.; Busatto, G.F. Neuroimaging in Alzheimer’s disease: Current role in clinical practice and potential future applications. *Clinics* **2011**, *66*, 19–24. <https://doi.org/10.1590/S1807-59322011001300003>. ISSN 1807-5932.
4. Taiyeb Khosroshahi, M.; Morsali, S.; Gharakhanlou, S.; Motamedi, A.; Hassanbaghlou, S.; Vahedi, H.; Pedrammehr, S.; Kabir, H.M.D.; Jafarizadeh, A. Explainable Artificial Intelligence in Neuroimaging of Alzheimer’s Disease. *Diagnostics* **2025**, *15*, 612. <https://doi.org/10.3390/diagnostics15050612>.
5. Mohsen, S. Alzheimer’s disease detection using deep learning and machine learning: A review. *Artif. Intell. Rev.* **2025**, *58*, 262. <https://doi.org/10.1007/s10462-025-11258-y>.

6. Athar, M.; Tufail, A.B.; Alyas, T.; Karnyoto, A.S.; Sheeraz, M.; Ibrahim, A.M.; Ghazal, T.M. Early diagnosis of alzheimer's disease using PET imaging and deep learning with comparative data augmentation techniques. *Sci. Rep.* **2026**, *16*, 660. <https://doi.org/10.1038/s41598-025-28866-x>.
7. Hatami, M.; Yaghmaee, F.; Ebrahimpour, R. Improving Alzheimer's disease classification using novel rewards in deep reinforcement learning. *Biomed. Signal Process. Control* **2025**, *100*, 106920. <https://doi.org/10.1016/j.bspc.2024.106920>.
8. Pradeep Reddy, G.; Rohan, D.; Kareem, S.M.A.; Venkata Pavan Kumar, Y.; Purna Prakash, K.; Janapati, M. A Custom Convolutional Neural Network Model-Based Bioimaging Technique for Enhanced Accuracy of Alzheimer's Disease Detection. *Eng. Proc.* **2025**, *87*, 47. <https://doi.org/10.3390/engproc2025087047>.
9. Kumar, T.; Brennan, R.; Mileo, A.; Bendeche, M. Image Data Augmentation Approaches: A Comprehensive Survey and Future Directions. *IEEE Access* **2024**, *12*, 187536–187571. <https://doi.org/10.1109/ACCESS.2024.3470122>.
10. Alruily, M.; Abd El-Aziz, A.A.; Mostafa, A.M.; Ezz, M.; Mostafa, E.; Alsayat, A.; El-Ghany, S.A. Ensemble deep learning for Alzheimer's disease diagnosis using MRI: Integrating features from VGG16, MobileNet, and InceptionResNetV2 models. *PLoS ONE* **2025**, *20*, e0318620. <https://doi.org/10.1371/journal.pone.0318620>.
11. Asaduzzaman, M.; Alom, M.K.; Karim, M.E. ALZENET: Deep learning-based early prediction of Alzheimer's disease through magnetic resonance imaging analysis. *Telemat. Inform. Rep.* **2025**, *17*, 100189. <https://doi.org/10.1016/j.teler.2025.100189>.
12. Muhammad, A.; Jin, Q.; Elwasila, O.; Gulzar, Y. Hybrid Deep Learning Architecture with Adaptive Feature Fusion for Multi-Stage Alzheimer's Disease Classification. *Brain Sci.* **2025**, *15*, 612. <https://doi.org/10.3390/brainsci15060612>.
13. Muksimova, S.; Umirzakova, S.; Baltayev, J.; Cho, Y.I. Multi-Modal Fusion and Longitudinal Analysis for Alzheimer's Disease Classification Using Deep Learning. *Diagnostics* **2025**, *15*, 717. <https://doi.org/10.3390/diagnostics15060717>.
14. Li, Y.; Niu, D.; Qi, K.; Liang, D.; Long, X. An imaging and genetic-based deep learning network for Alzheimer's disease diagnosis. *Front. Aging Neurosci.* **2025**, *17*, 1532470. <https://doi.org/10.3389/fnagi.2025.1532470>.
15. Chua, J.; Li, C.; Antochi, F.; Toma, E.; Wong, D.; Tan, B.; Garhöfer, G.; Hilal, S.; Popa-Cherecheanu, A.; Chen, C.L.; et al. Utilizing deep learning to predict Alzheimer's disease and mild cognitive impairment with optical coherence tomography. *Alzheimer's Dement.* **2025**, *17*, e70041. <https://doi.org/10.1002/dad2.70041>.
16. Zhou, J.; Wei, Y.; Li, X.; Zhou, W.; Tao, R.; Hua, Y.; Liu, H. A deep learning model for early diagnosis of alzheimer's disease combined with 3D CNN and video Swin transformer. *Sci. Rep.* **2025**, *15*, 23311. <https://doi.org/10.1038/s41598-025-05568-y>.
17. Mousavi, S.M.; Moulaei, K.; Ahmadian, L. Classifying and diagnosing Alzheimer's disease with deep learning using 6735 brain MRI images. *Sci. Rep.* **2025**, *15*, 22721. <https://doi.org/10.1038/s41598-025-08092-1>.
18. Ahamed, M.K.U.; Hossen, R.; Paul, B.K.; Hasan, M.; Al-Arashi, W.H.; Kazi, M.; Talukder, A. A hybrid filtering and deep learning approach for early Alzheimer's disease identification. *Sci. Rep.* **2025**, *15*, 27694. <https://doi.org/10.1038/s41598-025-03472-z>.
19. Rahman, S.; Rahman, M.M.; Bhatt, S.; Sundararajan, R.; Faezipour, M. NeuroNet-AD: A Multimodal Deep Learning Framework for Multiclass Alzheimer's Disease Diagnosis. *Bioengineering* **2025**, *12*, 1107. <https://doi.org/10.3390/bioengineering12101107>.
20. Vo, T.; Ibrahim, A.K.; Zhuang, H. A Multimodal Multi-Stage Deep Learning Model for the Diagnosis of Alzheimer's Disease Using EEG Measurements. *Neurol. Int.* **2025**, *17*, 91. <https://doi.org/10.3390/neurolint17060091>.
21. Razavi, S.M.; Tran, T.M.; Wilson, S.E.; Khanmohammadi, S. Brain State Transition Disruptions in Alzheimer's Disease: Insights from EEG State Dynamics. In Proceedings of the 2025 IEEE 22nd International Symposium on Biomedical Imaging (ISBI), Houston, TX, USA, 14–17 April 2025; pp. 1–5. <https://doi.org/10.1109/ISBI60581.2025.10981035>.
22. Wang, J.-L.; Sha, X.-Y.; Shao, Y.; Zhang, Z.-H.; Huang, S.-M.; Lin, H.; Gan, S.-Y.; Zhang, N.; Xia, X.-Y.; Sun, Y.-N.; et al. Elucidating pathway-selective biased CCKBR agonism for Alzheimer's disease treatment. *Cell* **2025**, *189*, 640–658.e22.
23. Petersen, R.C.; Aisen, P.S.; Beckett, L.A.; Donohue, M.C.; Gamst, A.C.; Harvey, D.J.; Jack, C.R., Jr.; Jagust, W.J.; Shaw, L.M.; Toga, A.W.; et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology* **2010**, *74*, 201–209. <https://doi.org/10.1212/WNL.0b013e3181cb3e25>.
24. Khagi, B.; Kwon, G.-R. 3D CNN Design for the Classification of Alzheimer's Disease Using Brain MRI and PET. *IEEE Access* **2020**, *8*, 217830–217847. <https://doi.org/10.1109/ACCESS.2020.3040486>.
25. Tartaglia, M.C.; Rosen, H.J.; Miller, B.L. Neuroimaging in Dementia. *Neurotherapeutics* **2011**, *8*, 82–92. <https://doi.org/10.1007/s13311-010-0012-2>.
26. Mattoli, M.V.; Cocciolillo, F.; Chiacchiarretta, P.; Dotta, F.; Trevisi, G.; Carrarini, C.; Thomas, A.; Sensi, S.; Pizzi, A.D.; Nicola, A.D.D.; et al. Combined 18F-FDG PET-CT markers in dementia with Lewy bodies. *Alzheimer's Dement* **2023**, *15*, e12515. <https://doi.org/10.1002/dad2.12515>. PMID: 38145190; PMCID: PMC10746864.

27. Silva-Rodríguez, J.; Labrador-Espinosa, M.A.; Moscoso, A.; Schöll, M.; Mir, P.; Grothe, M.J. For the Alzheimer's Disease Neuroimaging Initiative. Characteristics of amnesic patients with hypometabolism patterns suggestive of Lewy body pathology. *Brain* **2023**, *146*, 4520–4531. <https://doi.org/10.1093/brain/awad194>.
28. Gan, J.; Shi, Z.; Zuo, C.; Zhao, X.; Liu, S.; Chen, Y.; Zhang, N.; Cai, L.; Cui, R.; Ai, L.; et al. Analysis of positron emission tomography hypometabolic patterns and neuropsychiatric symptoms in patients with dementia syndromes. *CNS Neurosci. Ther.* **2023**, *29*, 2193–2205. <https://doi.org/10.1111/cns.14169>. PMID: 36924296; PMCID: PMC10352896.
29. Kantarci, K.; Boeve, B.F.; Przybelski, S.A.; Lesnick, T.G.; Chen, Q.; Fields, J.; Schwarz, C.G.; Senjem, M.L.; Gunte, J.L.; Jack, C.R.; et al. FDG PET metabolic signatures distinguishing prodromal DLB and prodromal AD. *Neuroimage Clin.* **2021**, *31*, 102754. <https://doi.org/10.1016/j.nicl.2021.102754>. PMID: 34252877; PMCID: PMC8278422.
30. Scheltens, N.M.E.; van der Weijden, K.; Adriaanse, S.M.; van Assema, D.; Oomen, P.P.; Krudop, W.A.; Lammertsma, A.A.; Barkhof, F.; Koene, T.; Teunissen, C.E.; et al. Hypometabolism of the posterior cingulate cortex is not restricted to Alzheimer's disease. *Neuroimage Clin.* **2018**, *19*, 625–632. <https://doi.org/10.1016/j.nicl.2018.05.024>. PMID: 29984170; PMCID: PMC6030576.
31. Whitwell, J.L.; Graff-Radford, J.; Singh, T.D.; Drubach, D.A.; Senjem, M.L.; Sychalla, A.J.; Tosakulwong, N.; Lowe, V.J.; Josephs, K.A. ¹⁸F-FDG PET in Posterior Cortical Atrophy and Dementia with Lewy Bodies. *J. Nucl. Med.* **2017**, *58*, 632–638. <https://doi.org/10.2967/jnumed.116.179903>. PMID: 27688479; PMCID: PMC5373504.
32. Womack, K.B.; Diaz-Arrastia, R.; Aizenstein, H.J.; Arnold, S.E.; Barbas, N.R.; Boeve, B.F.; Clark, C.M.; DeCarli, C.S.; Jagust, W.J.; Leverenz, J.B.; et al. Temporoparietal hypometabolism in frontotemporal lobar degeneration and associated imaging diagnostic errors. *Arch. Neurol.* **2011**, *68*, 329–337. <https://doi.org/10.1001/archneurol.2010.295>. PMID: 21059987; PMCID: PMC3058918.
33. Cong, H.; Yuan, L.; Zheng, P.; Xu, X.; Dong, W.; Tian, D.; Yin, L.; Ma, Y.; Song, T.; Zhao, Y.; et al. ¹⁸F-FDG PET/CT Reveals Characteristic Prefrontal-Posterior Cingulate Hypometabolism in anti-AMPA Encephalitis to Understand Cerebral Function: Insights From an Eight-Patient Cohort. *CNS Neurosci. Ther.* **2025**, *31*, e70633. <https://doi.org/10.1111/cns.70633>. PMID: 41153078; PMCID: PMC12568521.
34. Stubby, E.T.; Razavi, S.M.; Khanmohammadi, S. Functional Connectivity Disruptions in Alzheimer's Disease: A Maximum Flow Perspective. In *Computational Advances in Bio and Medical Sciences, ICCABS 2023*; Bansal, M.S., Chen, W., Khudyakov, Y., Măndoiu, I.I., Moussa, M.R., Patterson, M., Rajasekaran, S., Skums, P., Thankachan, S.V., Zelikovsky, A., Eds.; Lecture Notes in Computer Science; Springer: Cham, Switzerland, 2025; Volume 14548. https://doi.org/10.1007/978-3-031-82768-6_20.
35. Acharya, M.; Deo, R.C.; Tao, X.; Datta Barua, P.; Devi, A.; Atmakuru, A.; Tan, R.-S. Deep learning techniques for automated Alzheimer's and mild cognitive impairment disease using EEG signals: A comprehensive review of the last decade (2013–2024). *Comput. Methods Programs Biomed.* **2025**, *259*, 108506. <https://doi.org/10.1016/j.cmpb.2024.108506>.
36. Gao, S.; Lima, D. A review of the application of deep learning in the detection of Alzheimer's disease. *Int. J. Cogn. Comput. Eng.* **2022**, *3*, 1–8. <https://doi.org/10.1016/j.ijcce.2021.12.002>.
37. Tufail, A.B.; Ullah, I.; Rehman, A.U.; Khan, R.A.; Khan, M.A.; Ma, Y.-K.; Khokhar, N.H.; Sadiq, M.T.; Khan, R.; Shafiq, M.; et al. On disharmony in batch normalization and dropout methods for early categorization of Alzheimer's disease. *Sustainability* **2022**, *14*, 14695. <https://doi.org/10.3390/su142214695>.
38. Tufail, A.B.; Ma, Y.-K.; Kaabar, M.K.A.; Rehman, A.U.; Khan, R.; Cheikhrouhou, O. Classification of initial stages of Alzheimer's disease through pet neuroimaging modality and deep learning: Quantifying the impact of image filtering approaches. *Mathematics* **2021**, *9*, 3101. <https://doi.org/10.3390/math9233101>.
39. Tufail, A.B.; Anwar, N.; Ben Othman, M.T.; Ullah, I.; Khan, R.A.; Ma, Y.-K.; Adhikari, D.; Rehman, A.U.; Shafiq, M.; Hamam, H. Early-stage Alzheimer's disease categorization using PET neuroimaging modality and convolutional neural networks in the 2d and 3d domains. *Sensors* **2022**, *22*, 4609. <https://doi.org/10.3390/s22124609>.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.