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Choroidal Morphological Changes: A Promising Avenue for Early Diagnosis of Neurocognitive Disorders

Pranab Hazra[1]*, Mainak Dey[1], Priyanka Bawaly[1], Ashis Kumar Dhara[2], Tushar Kanti Bera[2]

[1]Electronics and Communication Engineering, Narula Institute of Technology, India, [2]Electrical Engineering, National Institute of Technology, Durgapur, India. *Corresponding Author's Email: pranabhazra2007@gmail.com

Abstract

Neurocognitive Disorders (NCDs) pose a substantial public health challenge, demanding timely detection and intervention to enhance patient outcomes. Recent strides in medical imaging have unveiled choroidal morphological alterations as a novel avenue for early NCD diagnosis. This study investigates the effectiveness of deep learning algorithms, particularly Residual neural networks (ResNet) and Visual Geometry Group 19 (VGG19) architectures, in analyzing choroidal images to identify subtle morphological changes indicative of underlying neurodegenerative processes. A comprehensive dataset encompassing choroidal images from individuals with NCDs and healthy controls was employed for model training and evaluation. Among the architectures assessed, ResNet152 exhibited superior performance, achieving an impressive area under the curve (AUC) of 0.97 in distinguishing between NCD patients and healthy individuals. The findings suggest that choroidal morphological changes hold promise as a potential biomarker for early NCD detection and monitoring. Integration of deep learning-based choroidal morphology analysis into clinical practice has the potential to enhance early intervention strategies, thereby contributing to improved patient outcomes in neurocognitive disorders. This research underscores the importance of exploring innovative approaches for early diagnosis and management of NCDs, aiming to enhance the quality of life for affected individuals and alleviate the societal burden associated with these disorders. Further studies are warranted to validate the utility of choroidal morphology analysis in clinical settings and to elucidate its role in the broader context of NCD diagnosis and management.

Keywords: AUC, Choroidal Morphology, Neurocognitive Disorders, ResNet, VGG19.

Introduction

As the human eye is a sensory organ of the nervous system, this living organ manages the visual system of the body. There are various parts of our eye (cornea, lens, iris, retina, choroid, optic nerve etc) that can be affected due to Alzheimer's disease. There are 4.6 million people around the world who are new patients. Prevalence of the disease makes some estimation that 19% of the patients aged 75-84 years and 30-35% are people whose age is more than 85 years old (1). A small portion (<5%) have a genetic origin. Alzheimer's disease (AD) is such kind of disease that cannot be detected in the early stage. To detect AD, we need to examine the brain tissue or a biopsy or post-mortem which involves developing nonreversible neuronal and synaptic devolution to the cortical grey matter. Researchers have found that amyloid deposit in the retina plays an important role in detecting AD in the early stage (2). Some researchers reported that choroid had been measured by enhanced depth imaging (EDI) and optical coherence tomography (OCT), it required approximately five years for initial academic work, using this technique to assess choroidal thickness (CT) in patients with AD for publication (3). Choroidal broadness is reduced in patients with AD compared to other eye patients which is analysed by Cunha et al. 90% of AD patients are positively marked with congophilic angiopathy, which is an initial pathological indicator of the disease' progression. We utilized various imaging modalities and measuring methodologies to evaluate choroidal morphology. The imaging modalities employed include Optical Coherence Tomography (OCT), which uses light waves to create detailed cross-sectional images of the retina and choroid. Within OCT, Spectral-domain OCT (SD-OCT) provides high-resolution images quickly, while Enhanced Depth Imaging OCT (EDI-OCT) is specifically designed to visualize deeper structures like the choroid. Another

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modality, Swept-Source Optical Coherence Tomography (SS-OCT), uses a longer wavelength light source than SD-OCT, allowing for deeper penetration and better visualization of the choroid. This technique is particularly useful for detailed mapping and volumetric analysis of the choroid, especially in patients with opaque media or thicker retinas. Additionally, B-Scan ultrasound utilizes sound waves to create images of ocular structures and is valuable when OCT cannot penetrate, such as with dense cataracts, providing essential information on choroidal thickness and structural abnormalities. Indocyanine Green Angiography (ICGA) employs indocyanine green dye and infrared light to visualize choroidal blood vessels, primarily used to study choroidal circulation and detect vascular abnormalities, offering critical insights into the vascular components of the choroid.

The measuring methodologies used in our study include choroidal thickness measurement, which involves measuring the distance between the outer border of the retinal pigment epithelium and the inner scleral surface, commonly performed using EDI-OCT and SS-OCT through manual or automated segmentation of choroidal boundaries in OCT images. Choroidal volume measurement quantifies the choroidal tissue volume within a defined area using volumetric scans with SS-OCT, involving segmentation of the choroid in 3D OCT datasets and integrating the area to obtain volume. The vascularity index, calculated using OCT and ICGA, represents the ratio of vascular area to the total choroidal area, indicating vascular density. Finally, choroidal structure analysis involves a detailed examination of choroidal layers and vasculature using high-resolution OCT and advanced image processing techniques. Alterations in choroidal morphology, such as thinning or vascular changes, are linked to the early stages of neurocognitive disorders. Regular imaging helps monitor disease progression and treatment effectiveness, providing valuable insights into the pathophysiology of these conditions. The disruption of the normal performance of the neurovascular unit occurs due to the loss of smooth muscle cells, leading to deterioration in the regulation of local blood flow caused by decreased vascular contractility and partial occlusion in the smaller distal Arteriole by Aβ aggregates (4). Reduction in the vascular density, blood flow in the brain and vascular thickness has been associated with these changes. Individuals diagnosed with Alzheimer's disease exhibited a notable decrease in the thickness of the choroid compared to healthy individuals. For both the diagnosis and monitoring of the disease, choroidal thinning could serve as an additional biomarker (5). Indeed, there is a consequential association between the brain and the eye. The insights gained from studying the retina can be instrumental in understanding the brain in both healthy and diseased states, given the many similarities shared between the retina and the brain. They have a common embryological origin that extends from the neural tube (6). The retina is a part of the central nervous system (CNS) and displays typical characteristics of the brain. Now, we reconnect the discovery regarding choroidal thickness and change in the retina due to beta-amyloid deposition (7). Abnormalities like pathological change, disc pallor, optic atrophy, and disc cupping may occur due to AD. The concept of utilizing the retina as a potential diagnostic tool for Alzheimer's disease has emerged as an innovative idea that is being more extensively researched (8).

In Table 1, we discuss how optometrists can contribute to the early detection of disease (1). This table outlines the current scenario of diagnosing Alzheimer’s disease through the presence of choroidal neovascularisation (CNV). It provides an overview of recent research findings, diagnostic methods, and the relevance of CNV as a potential biomarker. This summary helps in understanding the advancements and challenges in using CNV for early and accurate Alzheimer’s disease diagnosis. The use of PET and MRI methods, which are inexpensive and easy-to-use clinical tests, can be arranged to identify ocular and visual information that may serve as biomarkers (2). A 2021 review paper from the National Library of Medicine discusses a non-invasive process by which eye imaging has been used to detect Alzheimer’s disease in its early stages (3). An article accepted in Molecular Neurobiology in 2018 suggests that the MMSE method yields 82% accuracy, and it highlights the retina's potential as a window to the brain for early AD detection. This article also explores the application of animal models, specifically mouse models (4). Additionally, the mini-mental state examination (MMSE) can help in the development of a narrative colour vision threshold test known as RGB-vision plate (9),

which detects deficits in colour detection in AD patients and serves as a biomarker (5). A research article published in PLOS ONE in 2020 employs the enhanced depth imaging OCT (EDI-OCT) method to evaluate choroidal broadness in prodromal AD (7). A 2016 review article demonstrates a remarkable interconnection between CT values at various locations and MMSE scores (8). The table encompasses articles discussing ocular vascular changes through fluid and imaging tests of the eye, emphasizing the clinical application of ocular biomarkers. An article published by MDPI in 2021 presents a collaborative analysis of the Foveal Avascular Zone (FAZ) and OCT via eye imaging (10). Moreover, the American Journal of Ophthalmology published an article in 2021 demonstrating differences in choroidal structural parameters in eyes diagnosed with AD (11). Chorioretinal thickness measurement using methods such as SD-OCT and RTVue-100 can aid in AD observation (12, 13). A study employing neuropathological testing to assess tissue demonstrates the histomorphometry analysis of choroidal thickness and vascularity in severe AD (14). Various analysis indicates that the scattered ganglion cell layer in the preliminary stage of Alzheimer's can be assessed using OCT (15, 16). Early identification of neurocognitive disorders is crucial as it allows for timely interventions, which can significantly slow disease progression, enhance quality of life, and improve overall outcomes for patients. Prompt diagnosis facilitates the initiation of therapeutic strategies that can mitigate symptoms and possibly alter the disease direction which enables better planning and support for patients and their families, reducing the overall burden of the disease.

The study demonstrates the potential of choroidal morphological abnormalities as a reliable biomarker for early diagnosis of neurocognitive disorders. Changes in the choroid layer's structure, as identified through advanced imaging techniques, can reflect underlying neurodegenerative processes. These findings suggest that choroidal morphology can serve as an accessible and non-invasive indicator. The early detection of neurocognitive disorders is of paramount importance and this study supports the use of choroidal morphological changes as a promising and dependable biomarker.

The Alzheimer's Association published a research article in 2021 exploring Retinal and choroidal changes in men compared to those in women with Alzheimer's disease (17, 18). A longitudinal analysis of the retina and choroid in normal individuals, published in 2022, indicates evidence of differences in CST, PD , and peri-papillary CFI (19). An original investigation published by JAMA Ophthalmology in 2021 suggests an association between retinal changes and AD using the PiB-PET method (20). The Asia-Pacific Journal of Ophthalmology published a review article in 2022 discussing the association of retinal imaging with Alzheimer's disease (21). An article from Biomedicine published in 2023 utilizes the OCTB-scan method for image processing to detect neurodegenerative diseases (22). In a recent article from the Alzheimer's Association in 2023, the meta-analysis (PRISMA 2020) method was used for retinal imaging, focusing on brain amyloid status (23). A research article from Sage Journals discusses fundus examination, OCT, and OCT-A, which can focus on the presence of hyper-reflective deposits in AD (24). Frontiers published an article in 2023 discussing the association between retinal thinning and hippocampal atrophy in AD using various analyses and meta-regression methods (25). Additionally, the association of AD biomarkers and their roles in artificial intelligence was studied in a review paper from SpringerLink in 2023 (26).

Table 1: Current Scenario Regarding Alzheimer's Disease Diagnosis Using Choroidal Neovascularization (CNV)

Ref. no.	Year of publication	Methods	Eye Region	Contributions	Limitations
(1)	2009	Motility test(Binocular Exam)	Infront of Eye	Optometrists can help to identify AD through various determinations.	There should some more specific identification methods.
(2)	2013	PET and MRI	Inside eye	Inexpensive, userfriendly optical test to determine AD.	Only AD related problems are not classified particularly.
(3)	2021	Protein retinal imaging by OCT(Optical Coherence Tomography)	Imaging of Eye	Non-invasive, envisioning of retinal area.	Need to be a more specific maker.
(4)	2019	MMSE		Application of animal model	Early diagnosis method required.
(5)	2022	MMSE(Mini Mental State Examination)		Developed a novel Color detection test called RGB- vision plate.	The diagnostic accuracy of the RGB-vision test is required here.
(7)	2020	EDI- OCT	Scanning of eye	Progressive thinning in the choroid in the dementia stage	Could be more specific about the prodromal stages of AD.
(8)	2016	MMSE, OCT, HD-OCT, EDIOCT	Eye imaging	A significantly positive correlation was separately observed between the CT values at all localizations and the MMSE scores.	Measuring CT manually using EDI-OCT is believed to potentially introduce measurement errors.
(10)	2021	CSF ,MRI, PET ,OCT	Fluid and imaging test of eye	Emphasizes the clinical use of ocular biomarkers for predicting and diagnosing AD.	There is no analysis of clinical application.
(11)	2021	MMSE	Eye Imaging	Collaborated analysis of FAZ with OCT.	There are currently no observable ocular vascular changes associated with a genetic predisposition to Alzheimer's disease (AD).
(12)	2021	HD EDI foveal scan	Eye and Brain scanning	Showed that choroidal structural parameters may vary between the eyes of individuals	Longitudinal data should be helpful for better result.

				diagnosed with AD.	
(13)	2014	SD-OCT (RTVue- 100)	Retina scanning	Significant correlations between the mGCC thickness measurements of the AD observed.	No significant correlation between the MMSE scores and the CT measurements.
(14)	2019	Neuropathological test	Testing the tissue	Histomorphometri c analysis of both choroidal broadness and blood vessel density in advance AD.	Histological comparisons need to compare the results.
(15)	2021	(OCTA)	In the eye	Study with Electroretinograms.	The study of vessel parameter should be more descriptive.
(16)	2019	Optical coherence tomography scanning	In the eye	There is a significant link between the eye and the brain.	In-depth study requires longitudinal measurements and disease-specific imaging of both early-stage and latestage Alzheimer's disease (AD).
(17)	2021	OCT CT	In the Eye	Comprehensive analysis undertaken by separating all the 25 OCT B- scans per posterior EDI scans.	Brain imaging can be Elucidating whether the Observed choroidal thickening in pwDS results from developing AD.
(18)	2022	OCT and OCT angiography	In the eye	Showed that the sex of the patient is not linked to the micro vascular density in the retinas of patients with AD.	Need more contribution about the biomarkers.
(19)	2022	OCT and OCTA	In the eye	Preliminary findings suggest variances in the CST, PD, and peripapillary CFI between individuals with normal cognition who are carriers and noncarriers of the APOE ε4 gene.	Need more data relative to these.
(20)	2021	Pittsburgh compound B positron	In the eye and brain	Retinal biomarkers could serve as a method for screening for early	More information needed to Verify the study in detail.

		emission tomography ([11C] PiB-PET) and MRI		detection of AD.	
(21)	2022	Polyene chromophore imaging by PET	Inner eye	Retinal biomarkers for the diagnosis of Alzheimer's disease have revealed intriguing connections between retinal imaging results and AD.	Specialized noninvasive retinal imaging and computer processing power are necessary for identifying retina biomarkers.
(22)	2023	OCT B-scan	On the anesthetized eye	Implementation of image-processing techniques for Advancing the knowledge.	Can be more descriptive in vascular system.
(23)	2023	Meta-Analyses (PRISMA 2020)	In the retina	Implementation of meta-analysis on retinal image for the study of AD.	The experiment was done on retinal images and not includes any Diversity of perticipients (age, gender, ethnicity etc).
(24)	2023	Fundus examination, OCT and OCT-A	In the retina	OCT has the potential to reveal hyper reflective deposits present in Alzheimer's disease	Need some more information to analyse.
(25)	2023	Meta-Analysis (PRISMA)	Retinal image	Conduct a meta analysis on the correlation betweer retinal thickness and hippocampal volume.	The data on Alzheimer's disease is grouped with data from individuals with mild cognitive impairment (MCI) and those with normal cognition (NC). Access to the data of Alzheimer's disease patients separately is unavailable.
(26)	2023	Searching		Leveraging AI alongside ocular biomarkers in multimodal imaging has the potential to enhance the precision of identifying patients with Alzheimer's disease.	Additional research need on this topic.
(27)	2024	Korean version of the (MMSE) and detailed	Screening of eye and brain	The research showed that enlargement of the choroid plexus (CP) was	Retrospective crosssectional study; as such, causal relationships

		neuropsychological tests.		evident in patients along the Alzheimer's disease continuum. This enlargement was linked to heightened Aβ deposition and notable impairments in memory as well as frontal/executive function among these patients.	could not be demonstrated. AD is not discussed particularly.
(28)	2023	Neurologic and ophthalmologic examination and OCTA scans.	Neurologic and ophthalmologic examination and OCTA Scans.	OCTA offers accumulating evidence regarding the micro vascular alterations in the retina and choriocapillaris among patients with Alzheimer's disease.	OCTA software is Required to evaluate more precisely.
(29)	2021	OCTA and SPECTRALIS OCT	In the retina	Variances were observed in the retinal microvasculature among individuals with different APOEε4 statuses.	The small sample size may have led to a lack of statistically significant findings in certain analyses.
(30)	2022	OCT	In the retina	Showing an increase in IPL thickness in asymptomatic middle-aged individuals at high risk for Alzheimer's disease due to APOE Ɛ4, highlights the IPL as a particularly responsive retinal layer to early neurodegenerative changes associated with AD.	The absence of amyloid or tau imaging in both the retina and the brain hinders the investigation into whether these pathologies serve as the underlying mechanisms for the connection between APOE and retinal thickness.
(31)	2019	Commercial OCT	Study of retina	Centred on exploring the challenges and opportunities linked with utilizing OCT technology to detect biomarkers of Alzheimer's disease in the eye.	Reviewed only cross-sectional data.

An original article from the Aging and Disease Association in 2024 employs the Korean version of MMSE and detailed neuropsychological tests to demonstrate CP enlargement in AD patients (27). In 2023, the Journal of Neuro-ophthalmological contributed an article providing evidence of microvascular changes in the retina and chorio-capillaries in patients with AD (28). A study published in Scientific Reports in 2021 explores retinal thickness in association with apolipoprotein E genotype in AD (29). Lastly, the Alzheimer's Association demonstrated in a research article in 2022 that IPL thickening in asymptomatic middle-aged individuals may indicate a high risk of AD (30). The National Library of Medicine published a PMC article in 2019 discussing a recent analysis of the detection of Alzheimer's disease (31).

The study offers a unique contribution by demonstrating the link between choroidal morphological changes and neurocognitive disorders. This interdisciplinary approach highlights how ophthalmological assessments can

provide critical insights into neurological health. By identifying specific choroidal changes associated with neurocognitive decline, the study bridges between these two fields, showcasing the eye as a window to brain health (32). The value of our findings lies in the potential for early diagnosis and intervention. Utilizing choroidal morphology as a biomarker for neurocognitive disorders can lead to earlier detection and treatment, ultimately improving patient outcomes. This novel approach not only advances the field of ophthalmology by expanding its diagnostic capabilities but also contributes significantly to neurology by offering a new, non-invasive method to identify at-risk individuals. This interdisciplinary link provides a valuable foundation in clinical practice, enhancing the ability to diagnose and treat neurocognitive disorders more effectively.

The manuscript includes a comprehensive review of recent publications that explore the relationship between choroidal morphology and neurocognitive disorders. This is detailed in Table 1, which summarizes the most relevant and recent studies, highlighting their contributions to understanding how changes in choroidal structure may indicate neurocognitive decline. The reference list also includes current research, providing a broader context and reinforcing the current knowledge base on this topic. These updates ensure that our study is aligned with the latest advancements and reflects the most recent evidence available. We have incorporated current research findings and updated our references to accurately represent the ongoing developments in the connection between choroidal morphology and neurocognitive diseases.

Methodology

The data was uploaded to a drive and connected to the model at the backend. We utilized tensorflow and 2D convolution for data processing. The data was divided into training, validation, and test sets. Following the training process, VGG19 and ResNet were employed for improved classification. 'RMSProp' was used as the optimizer, resulting in a well-organized dataset with dimensions of 224 x 224. Image processing involved a zoom range of 0.12 and a shift range of 0.15, resulting in images of 224 x 224 dimensions in JPG format (33). The images were converted to grayscale, as illustrated in Figure 1 and Figure 2. This processing technique simplifies the visual data by using shades of grey, which helps emphasize important features and reduce computational complexity. This experiment was conducted on Google Collaboratory using TensorFlow and Keras in the backend. Each image was input into the convolution layers of VGG19 and ResNet for further processing. In our study, we have gathered colloidal images of individuals both diagnosed with Alzheimer's disease (as depicted in Figure 1) and those unaffected (as depicted in Figure 2). The dataset comprises images of early-stage Alzheimer's patients and healthy individuals. Pre-processing of the dataset is essential to enhance data stability and eliminate noise. Techniques such as data augmentation, image segmentation, noise reduction, and resizing are employed for image processing (34). By pre-processing the dataset, we can effectively train the chosen deep learning method.

We selected our study population based on the need to investigate choroidal morphological changes as a potential early diagnostic marker for neurocognitive disorders. The chosen population includes individuals at different stages of neurocognitive decline, as well as healthy controls, to provide a comprehensive comparison. This approach allows us to examine the relationship between choroidal morphology and neurocognitive status across a spectrum, thereby enhancing the study's relevance and applicability. By including participants with varying degrees of cognitive impairment, we aim to identify specific choroidal changes that may serve as early indicators of neurocognitive disorders.

Participants aged 50-80 years were chosen because this age group is most commonly affected by neurocognitive disorders. We included individuals with mild cognitive impairment (MCI) or early-stage Alzheimer's disease, as well as healthy controls, to serve as a baseline. All participants must provide informed consent and undergo necessary imaging procedures.

We excluded individuals with advanced neurocognitive disorders, ocular conditions (e.g., age-related macular degeneration, diabetic retinopathy), and significant systemic diseases (e.g., uncontrolled hypertension, diabetes) to ensure observed changes are related to neurocognitive status. Participants unable to comply with imaging procedures or provide reliable data were also excluded. The data must be divided into training, validation, and testing sets to

monitor model performance. Early detection necessitates timely classification of the data. Proper exploration of the data can reveal differences in colloidal thickness aiding in the identification of early signs and biomarkers (7), (8) and (10). Evaluation of the dataset through various scaling methods and modelling functions allows for the assessment of the Evaluation Matrix and the generation of the receiver operator characteristics curve (27). Implementation of AUC-ROC cross-validation is crucial to enhance the model's applicability and robustness. As this is experimental work, evaluating the trained model's performance on an external dataset is necessary to ensure its effectiveness within critical communities (35). Additionally, exploring visualization techniques can significantly contribute to the preliminary detection process of Alzheimer's disease.

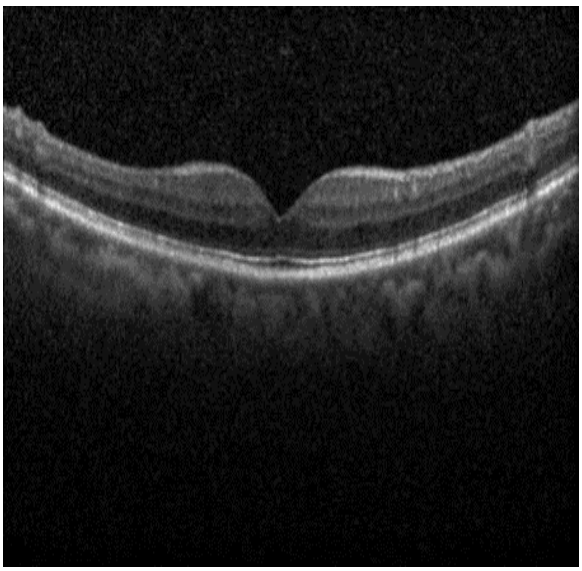

Figure 1: CNV Normal

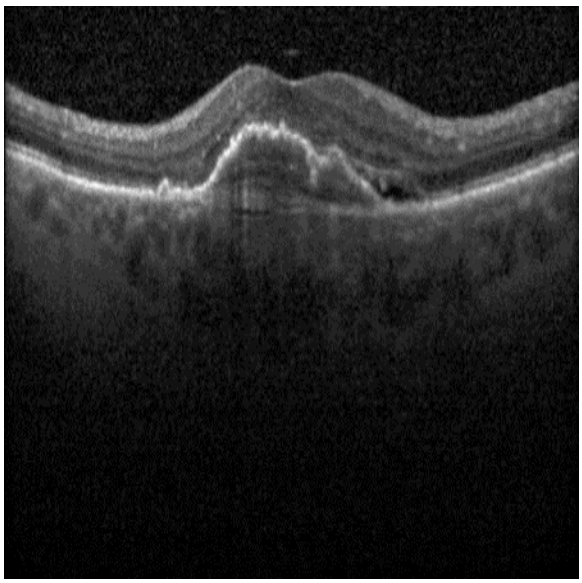

Figure 2: CNV Effected

Figure 3 depicts the overview of the system framework and illustrates its key components and their interactions. This diagram provides a detailed visualization of how each part of the system connects and collaborates, ensuring seamless functionality. It highlights the data flow between modules and the integration of various processes. This comprehensive view helps in understanding the system's overall architecture and operational dynamics.

ResNet and VGG19 are top choices for Alzheimer's disease detection due to their deep architectures, proven performance, and unique advantages. ResNet's introduction of residual connections tackles training challenges in deep networks, while pre-trained versions improve performance with limited data. VGG19's simpler architecture has shown outstanding results across diverse computer vision tasks (36), promising accurate identification of Alzheimer's disease indicators. Their effective feature learning and resource efficiency make them strong contenders for precise diagnoses from medical imaging data. Table 2 summarizes the diverse architectures, performance metrics and advantages of various models. It provides a comparative analysis highlighting each model's unique structural features, effectiveness, and specific benefits. This table serves as a comprehensive resource for understanding the strengths and weaknesses of different models.

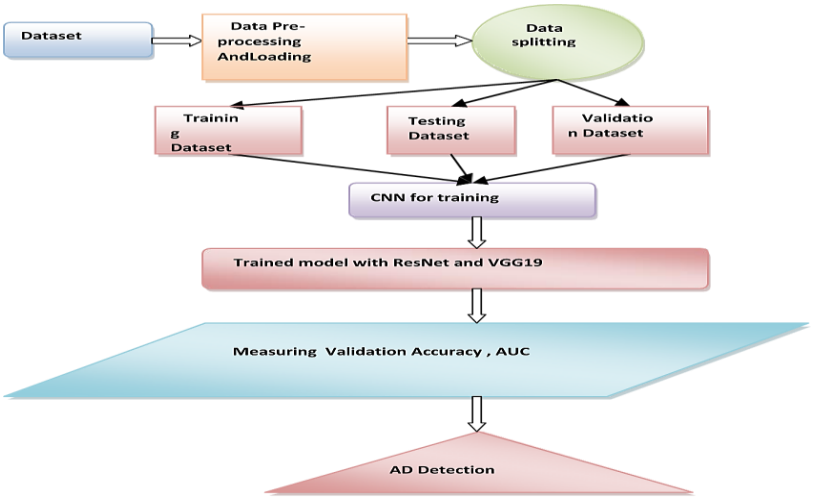

Figure 3: Overview of the System Framework, Illustrating Key Components and Their Interactions

Table 2: The Diverse Architecture, Performance and Advantages of Various Models

Model Name	Layers	Depth of Architecture	Performance	Advantages
AlexNet	8	It is a pioneering deep convolutional neural network, boasts a relatively Shallow architecture compared to later models.	It's innovative architecture, including convolutional and fully connected layers, along with techniques like dropout regularization, demonstrated significant advancements in image classification accuracy.	1. Innovative deep convolutional architecture. 2. Effective regularization with dropout. 3. Utilization of parallel processing for faster training.
ResNet 18 ResNet 50 ResNet 101 ResNst 152	18 50 101 152	ResNet is relatively deep architectures. ResNet introduces residual connections to facilitate the training of very deep networks.	ResNet has demonstrated state-of-the-art performance on various computer vision tasks.	1. It introduced residual connections, which allow for very deep networks (hundreds of layers) to be trained effectively. 2. It serves as a powerful solution to mitigate the vanishing gradient issue commonly encountered during training. 3. Pre-trained versions of ResNet on largescale datasets are readily available which improves the
VGG 19	19	VGG19 is relatively deep architectures. VGG19 follows a simpler	It has showcased cutting-edge performance across a	

	architecture with stacked convolutional layers and pooling layers.	spectrum of computer vision challenges	performance with less data and computational resources.
InceptionV3 InceptionResNetV2	These models utilize inception modules, which are efficient at capturing multi- scale features by using different kernel sizes within the same layer.	Models have competitive performance, specially in tasks requiring multi-scale feature extraction.	This can utilization of lead computational resources and improved performance, especially in scenarios with limited computational resources.

Results

The study investigates the potential of choroidal morphological changes as a novel avenue for the early diagnosis of neurocognitive disorders. Various deep learning models, including ResNet (18, 50, 101, and 152) and VGG 19, were employed to analyze choroidal images and assess their accuracy in classifying individuals with and without neurocognitive disorders. As the vanishing gradient problem can be overcome in these models, it is beneficial to use in this classification task. Table 3 presents the accuracy, sensitivity (SEN), specificity (SPE) (23)-(24) and AUC for the said deep learning models. These metrics serve as indicators of the models' performance in distinguishing between neurocognitive disorder cases and healthy controls based on choroidal morphology. To demonstrate the effectiveness of each module in our method, we will conduct ablation experiments. The method is compared with previous approaches to assess performance. This research suggests that choroidal morphological changes can serve as early biomarkers for neurocognitive disorders. Practically, this means that routine ophthalmological examinations could be adapted to include assessments of choroidal morphology, enabling early identification of individuals at risk for neurocognitive decline. This early detection could lead to timely interventions, potentially slowing the progression of these disorders and improving patient outcomes. Detecting neurocognitive issues at an early stage through non-invasive eye exams would allow healthcare providers to implement preventive measures and initiate treatments sooner. This proactive approach could involve lifestyle changes, cognitive therapies, or pharmacological treatments aimed at reducing the impact of neurocognitive disorders. Our research underscores the practical advantages of using choroidal morphological changes as biomarkers for the early diagnosis and treatment of neurocognitive disorders.

The experiments were carried out in a server environment equipped with an NVIDIA GeForce RTX 3040 Ti Laptop GPU using ADNI-sampled data. Implementation of our method was based on PyTorch, TensorFlow, Panda, and Python 3.5. The results align with the hypothesis that choroidal morphological changes could serve as reliable biomarkers for the early detection of neurocognitive disorders (4). The varying performance of different deep learning models suggests the importance of selecting an appropriate model architecture for optimal classification accuracy. The reported accuracy, sensitivity, specificity and AUC values demonstrate the statistically significant performance of the models in classifying individuals with neurocognitive disorders (5). The high AUC values (>0.8) indicate the strong discriminative ability of the models. ResNet152 exhibits the highest accuracy (96.52%), sensitivity (93.45%), specificity (95.67%), and AUC (0.97187), followed closely by ResNet101 (6). These findings suggest that deeper network architectures may capture more tangled patterns in choroidal morphology, leading to improved diagnostic performance. The relatively lower performance of ResNet50 compared to ResNet18 and VGG 19 highlights the importance of model selection and architecture optimization in deep learning-based medical image analysis tasks. Further exploration of the underlying reasons for these differences could provide valuable insights for future research.

The study confirms choroidal morphology as a potential biomarker for neurocognitive disorders (12, 15).

$$ACC = \frac{TP + TN}{TP + TN + FP + FN}, SEN = \frac{TP}{TP+FN}, SPE = \frac{TN}{TN+FP} \quad \text{.....[1]}$$

Table 3: Accuracy of Models Utilizing Choroidal Neovascularization for Alzheimer's Disease

Models	Accuracy ACC	Sensitivity (SEN)	Specificity (SPE)	AUC
ResNet 18	81.26%	80.22%	83.02%	0.83256 (83.256%)
ResNet 50	72.41%	70.69%	74.62%	0.77358 (77.358%)
ResNet 101	92.95%	91.54%	94.32%	0.95967 (95.967%)
ResNet 152	96.52%	93.45%	95.67%	0.97187 (97.187%)
VGG 19	85.26%	83.47%	87.33%	0.89486 (89.486%)

Deep learning models offer enhanced diagnostic accuracy compared to traditional methods. While promising, further validation on larger datasets is needed for universality. Longitudinal studies are essential to assess predictive value for disease progression. The study provides compelling evidence for using choroidal morphology in early diagnosis, emphasizing the potential of advanced computational techniques for improved patient outcomes. These findings pave the way for future research integrating choroidal imaging into clinical practice for neurocognitive disorder management.

We employed convolutional neural networks (CNNs), specifically ResNet and VGG19 architectures, to analyze choroidal morphological changes. These models are highly suitable for image classification and feature extraction, which are essential for identifying early signs of neurocognitive disorders. ResNet's residual learning helps in training deeper networks, while VGG19's structure provides a robust framework for detailed feature extraction, justifying their selection for our study.

Discussion

The findings of our study highlight the potential of choroidal morphological changes as an innovative approach for early neurocognitive disorder diagnosis. By employing a range of deep learning models, such as ResNet (18, 50, 101, 152) and VGG 19, we aimed to analyze choroidal images and evaluate their efficacy in distinguishing individuals with and without neurocognitive disorders (12). The study utilized ResNet 18, 50, 101, 152, and the VGG 19 model to analyze the accuracy, with varying results displayed in Table 2. Notably, ResNet152 demonstrated the highest accuracy in the detection process with AUC 0.97 as shown in Figure 5 in Resnet 152.

Figure 4 indicates the validation accuracies for ResNet (18, 50, 101, and 152) for AD classification but validation accuracy is not the perfect measurement of the accuracy for the model because it gives accuracy pointwise. So, once a model achieves maximum accuracy for a particular input image that is taken as the maximum accuracy of the model instead the model has poor performance for other input images.

Figure 4 indicates the training and validation accuracy of different ResNet and VGG models compared to assess their performance. This comparison highlights how each model learns from the training data and generalizes to new, unseen data. The results demonstrate the effectiveness of these architectures in achieving high accuracy, with variations indicating the strengths and weaknesses of each model type.

So, we must go with the help of the area under the receiver operating characteristic curve (AUC) as depicted in Figure 5, because it measures the same model's performance across different thresholds. The experimental results represent the significant accuracy achieved using the segmented CNV images conducted for all experiments separately (23). Throughout the study, the focus was on choroidal imaging for early AD detection. However, research gaps were identified, prompting the use of a residual network in the convolution neural network model to address these areas.

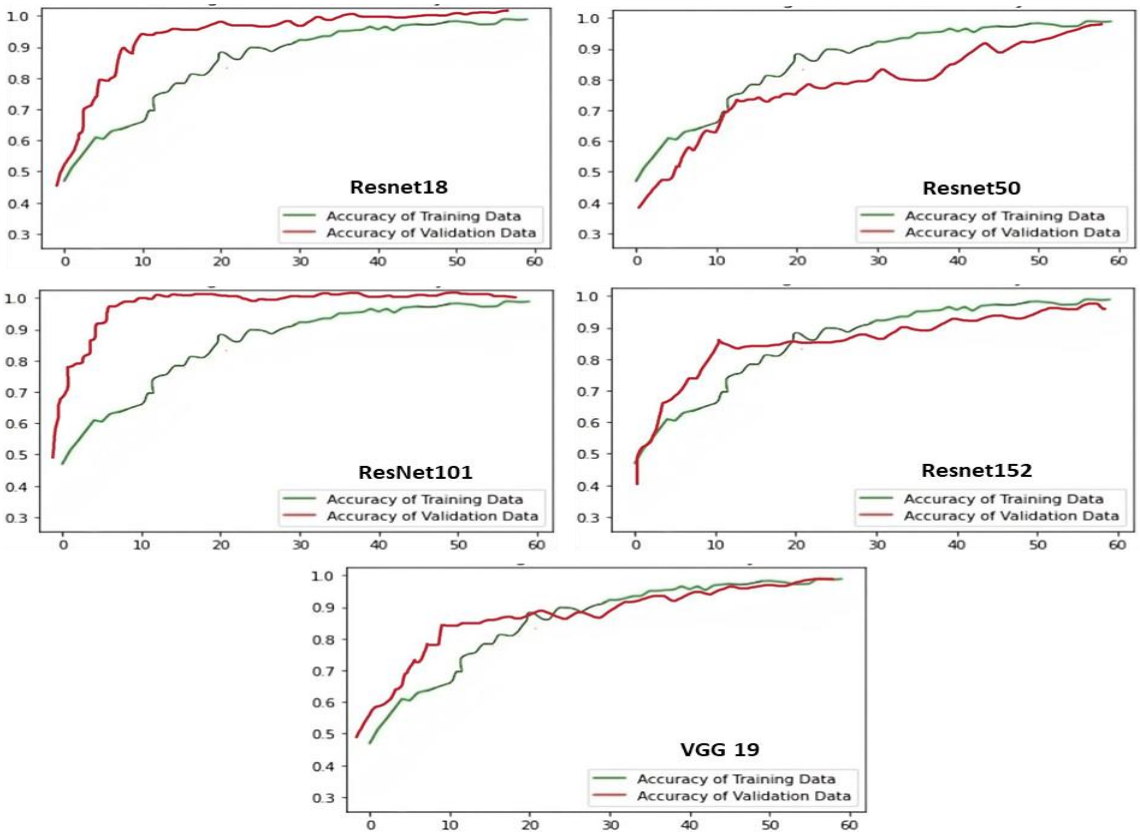

Figure 4. Training and Validation Accuracy of Different Types of ResNet and VGG Mode

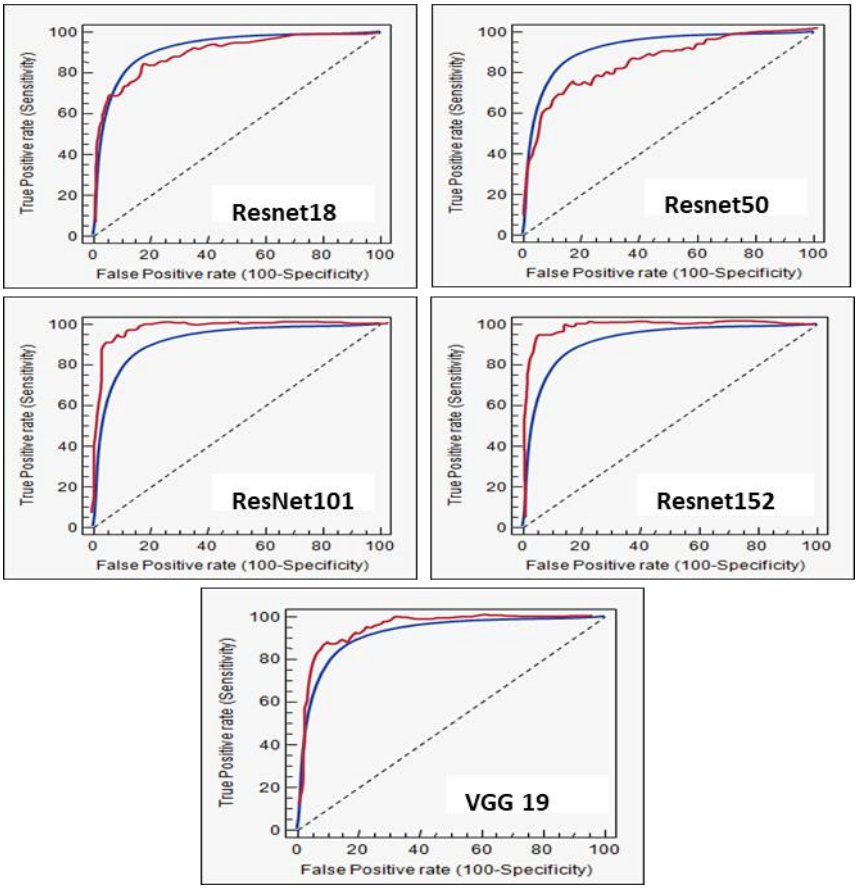

Figure 5. AUC Graph for Different ResNet and VGG Models

The results support the notion that choroidal morphological (11) alterations could serve as dependable biomarkers for early detection, underscoring the transformative role of advanced computational methods in medical image analysis. The varying performance of different deep learning models underscores the importance of selecting appropriate model architecture for optimal classification accuracy. Notably, ResNet152 emerged as the most promising model, exhibiting the highest accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) (10). These findings suggest that deeper network architectures may capture more intricate patterns in choroidal morphology, leading to improved diagnostic performance. The study has certain limitations that include variations in image quality and the need for further validation on larger and more diverse datasets to confirm the universality of our findings. It provides compelling evidence for the utility of choroidal morphological changes as a promising avenue for the early diagnosis of neurocognitive disorders (19).

Figure 5 displays the AUC (Area Under the Curve) graph for several ResNet and VGG models, offering a comparison of their classification performance. By illustrating the AUC values, this graph highlights each model's ability to accurately distinguish between classes. Higher AUC scores represent superior model performance, providing a clear visual assessment of the models' relative effectiveness. This study included a sample of 2400 individuals, which we believe is sufficient for detecting significant choroidal morphological changes related to neurocognitive disorders. However, we acknowledge that a larger sample size could provide more robust results and better generalizability. To address this, we performed data augmentation to ensure the sample size was adequate for the statistical methods used, and we plan to include more participants in future studies to validate our findings further. Our cohort included participants from diverse age groups, genders, and ethnic backgrounds. We stratified our sample to match the demographic distribution of the broader population, minimizing potential bias.

To mitigate selection bias, random sampling methods were used, with recruitment across multiple centres. Standardized imaging protocols and validated measurement tools were employed to reduce measurement bias. We controlled for potential confounding variables such as age, sex, and medical history using multivariable regression models and conducted sensitivity analyses to ensure result robustness. While some biases and limitations may remain, including the cross-sectional design limiting causality inference, we have transparently reported these in the manuscript. Despite our efforts, some biases and limitations might remain. For example, the cross-sectional design of the study limits our ability to infer causality. Additionally, while our sample was diverse, there may still be unmeasured confounders that we could not control for. We have transparently reported these limitations and discussed their potential impact on the interpretation of our findings.

The findings underscore the potential of advanced computational techniques in medical image analysis and lay the groundwork for future research aimed at integrating choroidal imaging into clinical practice for the effective management of neurocognitive disorders (20). Based on the outcome of the method, our method was done with the ResNet 18, 50,101,152 and the VGG19 models. We compare the numbers of total parameters, accuracy, and AUC of different types of attention modules. The results are shown above. From the above table, we can see that the ResNet 152 is the best network, in comparison with other combinations (21). It helps mostly in the detection of AD. We can find the highest accuracy of our method with a standard deviation of lower than the ResNet 152, in the detection of AD (22). In all combinations, we can use the multiple classes of data, for evaluation of the CNN models. We segmented the CNV images in our method and conducted all the experiments separately. The total number of the datasets we use is the highest of all other datasets. Compared with the other previous Research works, as shown in the table. In Table 3 we achieved the best AUC through the Resnet152 model which is 0.97. Based on this result we believe that this model has a better performance than other combinations for AD diagnosis. In our methodology, we achieved a better model than the other researchers our model gave a better result. Conducting replication studies with larger and more diverse cohorts would help authenticate our findings. This could include multi-centre studies that encompass varying demographics to ensure the results are generalizable across different

populations. Implementing longitudinal studies would provide insights into the temporal changes in choroidal morphology relative to the progression of neurocognitive disorders. Tracking these changes over time could help in understanding their diagnostic value and potential as biomarkers for early intervention. Conducting clinical trials that evaluate the effectiveness of using choroidal morphology as a diagnostic tool in clinical practice could provide valuable evidence for its utility. This could involve assessing patient outcomes based on early diagnosis facilitated by choroidal assessments. This study contributes significantly to the current understanding of neurocognitive disorders by demonstrating the potential of choroidal morphological changes as early biomarkers. This adds a novel dimension to the field, which traditionally relies on more invasive and expensive neuroimaging techniques. By providing a non-invasive and cost-effective method for early detection, our study offers a new avenue for research and clinical practice. Current diagnostic approaches for neurocognitive disorders often lack sensitivity in the early stages of the disease, leading to delays in diagnosis and treatment (38). Our study fills this gap by highlighting how routine ophthalmological examinations can be adapted to assess choroidal morphology, thereby facilitating early identification of at-risk individuals. The study not only enriches the existing body of knowledge by introducing choroidal morphological changes as a potential biomarker for neurocognitive disorders but also addresses critical gaps in current diagnostic methods.

The work is validated by several theoretical frameworks that explain the relationship between ocular biomarkers, such as choroidal morphological changes, and neurocognitive health. One prominent framework is the neurovascular hypothesis, which posits that neurodegenerative diseases like Alzheimer's involve disruptions in both cerebral and ocular vasculature (39). This theory suggests that changes in the choroidal structure, which shares similarities with the brain's vascular system, can reflect underlying neurocognitive changes.

Another relevant framework is the biomarker theory, which supports the use of ocular biomarkers as non-invasive indicators of systemic diseases. This theory provides a basis for using choroidal morphology to detect early signs of neurocognitive decline, signifying the fact that ocular changes can precede and correlate with cognitive impairments. These theoretical frameworks are significant in our study as they provide a conceptual basis for understanding how choroidal changes might indicate neurocognitive disorders. They guide our research design by justifying the focus on ocular biomarkers and help interpret our findings in the context of broader physiological and pathological processes.

Conclusion

We have demonstrated that the recognition and classification of Alzheimer's disease (AD) and healthy controls can be achieved not only through brain MRI images but also through Choroidal Neovascularisation (CNV) images, presenting another biomarker for AD detection. Studying CNV images is less complex compared to MRI images, facilitating potential diagnostic applications. Utilizing advanced deep learning techniques, notably ResNet152, our study has achieved the highest Area Under the Curve (AUC) of 0.97 among all ResNet and VGG19 models. This outcome underscores the robustness and effectiveness of our approach in neurocognitive disorder diagnosis. The intricate relationship between choroidal morphology and neurocognitive disorders provides a unique opportunity for early detection and intervention, potentially leading to enhanced patient outcomes and quality of life. By harnessing cutting-edge technologies such as deep learning, we have not only deepened our understanding of these morphological changes but also laid the foundation for the development of novel diagnostic tools with superior accuracy and efficiency. Collaborative endeavours among clinicians, researchers, and technologists will be vital in translating these findings into clinical practice, ultimately benefiting individuals at risk of neurocognitive disorders and advancing the field of neuroimaging diagnostics.

Abbreviations

NCD: Neurocognitive Disorder
AUC: Area Under Curve
AD: Alzheimer's Disease
Aβ: Amyloid Beta
PET: Positron Emission Tomography
MMSE: Mini-Mental State Examination
FAZ: Foveal Avascular Zone

OCTA: Optical Coherence Tomography Angiography
PD: Parkinson disease
APOE: Apolipoprotein E
MCI: Mild Cognitive Impairment
AI: Artificial Intelligence
IPL: Intense Pulsed Light
ResNet: Residual Network
JPG: Joint Photographic Experts Group
ACC: Accuracy
SPE: Specificity
CNV: Choroidal Neovascularization
EDI: Enhanced Depth Imaging
OCT: Optical Coherence Tomography
CT: Choroidal Thickness
CNS: Central Nervous System
MRI: Magnetic Resonance Imaging
RGBvision plate: Red Green Blue vision plate
SD-OCT: Spectral Domain Optical Coherence Tomography
CST: Central Subfield Thickness
CFI: Color Fundus Image
PiB-PET: Pittsburgh compound B Positron Emission Tomography
NC: Normal Cognition
CP: Choroidal Plexus
VGG: Visual Geometry Group
RMSprop: Root Mean Squared Propagation
AUC-ROC: Area under the Receiver Operating Characteristic Curve
SEN: Sensitivity
ADNI: Alzheimer's Disease Neuroimaging Initiative
CNN: Convolutional Neural Network

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Author Contributions

Pranab Hazra contributed to concept and data interpretation, Mainak Dey to Design, Priyanka Bawaly and Pranab Hazra to manuscript drafting, and Ashis Kumar Dhara and Tushar Kanti Bera provided final approval for publication.

Conflict of Interest

The authors have disclosed no conflicts of interest.

Ethics Approval

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