Review

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Review

Artificial Intelligence-Based Methods for Earlier Diagnosis and Personalized Management in Neuro-Ophthalmic and Neurodegenerative Disorders

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Abstract: Advancements in neuroimaging, particularly diffusion MRI techniques and molecular imaging via PET, have significantly improved our ability to detect early biomarkers of both neurodegenerative and neuro-ophthalmic disorders, such as Alzheimer's, Parkinson's, multiple sclerosis (MS), neuromyelitis optica (NMO), and myelin oligodendrocyte glycoprotein (MOG) antibody disease. Despite these breakthroughs, the integration of AI-driven models has become crucial in harnessing the full potential of these technologies for clinical decision-making. This paper explores the role of advanced diffusion MRI techniques—specifically Neurite Orientation Dispersion and Density Imaging (NODDI) and Diffusion Kurtosis Imaging (DKI)—in revealing microstructural changes in brain and visual pathway tissues that precede clinical symptoms. These techniques, when paired with AI algorithms, enhance diagnostic precision, enabling the detection of early-stage degeneration and inflammatory processes with unprecedented accuracy. Additionally, the emergence of next-generation PET tracers targeting misfolded proteins, such as tau and alpha-synuclein, and inflammatory markers, further augments our ability to visualize and quantify pathological processes in vivo. The integration of AI, particularly deep learning models like convolutional neural networks (CNNs) and multimodal transformers, has demonstrated remarkable success in improving diagnostic accuracy, combining data from multiple imaging modalities, and providing predictive insights into disease progression. This review also examines the challenges associated with integrating AI into clinical practice, including technical variability, data privacy concerns, and regulatory hurdles. While these technologies promise to revolutionize early diagnosis and personalized treatment approaches, significant efforts in model validation, standardization, and clinical implementation remain crucial. The ongoing development of AI-enhanced neuroimaging holds great potential for advancing the precision of diagnosis and the

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effectiveness of therapeutic interventions in both neurodegenerative and neuro-ophthalmic disorders.

Keywords: AI-driven ophthalmology; AI-driven therapy; neurodegenerative diseases; machine learning; neural modulation

Introduction

The early diagnosis and prognosis of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), as well as neuro-ophthalmic disorders like multiple sclerosis (MS), neuromyelitis optica (NMO), and myelin oligodendrocyte glycoprotein (MOG) antibody disease, represent some of the most pressing challenges in clinical neurology and ophthalmology [1–3]. These diseases typically progress insidiously, with subtle signs appearing long before significant clinical manifestations become evident [4,5]. In particular, conditions affecting both the central and peripheral nervous systems, including those impacting the visual pathways and ocular structures, often present with early symptoms such as optic neuritis or visual field defects that are frequently overlooked or misdiagnosed [6,7]. Early detection is critical to slowing or halting disease progression and improving patient outcomes.

Despite significant advancements in diagnostic tools, many of these conditions are diagnosed only after substantial neurological or visual decline has occurred, reducing the effectiveness of treatments [9,10]. Thus, identifying reliable biomarkers for early detection remains crucial in enabling timely intervention and improving the prognosis for affected patients [11,12]. Recent advancements in neuroimaging, particularly ultra-high-field magnetic resonance imaging (UHF-MRI) at 7 Tesla (T) and beyond, have significantly enhanced our ability to detect abnormalities with unprecedented precision [13,14]. These cutting-edge imaging systems can identify subtle structural changes, such as hippocampal atrophy in Alzheimer's disease, nigral degeneration in Parkinson's disease, or optic nerve atrophy in MS and NMO, long before they become clinically apparent [15,16]. Similarly, advanced diffusion tensor imaging (DTI) allows for the assessment of white matter integrity, revealing early microstructural damage in both brain and optic nerve tissues that previously went undetected [17,18].

These technologies provide critical insights for early diagnosis, but their effectiveness is often limited by the sheer complexity and volume of the data they generate. Artificial intelligence (AI) is revolutionizing the field of neuroimaging by offering sophisticated solutions to this data complexity [20,21]. Deep learning algorithms, including convolutional neural networks (CNNs) and transformer-based models, are increasingly capable of performing tasks such as brain and optic nerve segmentation, volume measurement, and pathology identification with exceptional accuracy—often surpassing human capabilities [22–24]. AI's integration with neuroimaging has unlocked new possibilities, particularly through the fusion of multimodal data—combining structural and functional MRI, positron emission tomography (PET), and genetic markers—into unified diagnostic models [25,26]. This approach allows for the early identification of neurodegenerative and neuro-ophthalmic changes in asymptomatic individuals, facilitating earlier interventions and potentially improving patient outcomes [27,28].

Furthermore, the development of next-generation PET tracers targeting amyloid plaques, tau, alpha-synuclein aggregates, and inflammatory markers has provided molecular insights into the pathological processes driving diseases like Alzheimer's, Parkinson's, and MS [29,30]. The synergy between advanced neuroimaging techniques and AI analytics enhances diagnostic accuracy and supports the development of personalized treatment strategies tailored to individual patients' neurobiological profiles [31,32]. While the potential of these technologies is substantial, their clinical implementation is still hindered by challenges such as data heterogeneity, the need for large-scale validation studies, and ethical concerns related to AI-driven systems [33–35]. This review explores the current landscape of advanced neuroimaging and AI technologies, highlighting their potential to

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transform the early detection, prognosis, and treatment of both neurodegenerative and neuro-ophthalmic disorders, while also addressing the obstacles that must be overcome to integrate these innovations into routine clinical practice.

Advances in Neuroimaging and AI Integration

I. Diffusion MRI Techniques

Diffusion tensor imaging (DTI) has been widely used for assessing the integrity of white matter, providing valuable insights into microstructural changes occurring in neurodegenerative and associated disorders [51,52]. DTI operates by measuring the anisotropic diffusion of water molecules along axonal fibers, serving as a proxy for the coherence and structural integrity of white matter tracts [53]. However, the limitations of DTI lie in its inability to disentangle overlapping microstructural changes in different tissue compartments, particularly in regions where axonal or cellular complexity is higher, such as in optic nerve and visual pathway structures. This shortfall has driven the evolution of more sophisticated diffusion imaging techniques [54].

Neurite Orientation Dispersion and Density Imaging (NODDI) builds upon DTI by employing a multi-compartment biophysical model to separately quantify neurite density and orientation dispersion [55]. This allows for a more detailed assessment of tissue microarchitecture and has proven especially useful in distinguishing subtle changes within structurally complex regions, such as those impacted by inflammatory and degenerative processes. NODDI enables the isolation of intracellular, extracellular, and isotropic diffusion components, facilitating the identification of early pathological changes. For example, in Parkinson's disease, NODDI has demonstrated higher sensitivity than DTI in detecting alterations in the substantia nigra, a key motor-related structure, and similar sensitivity may extend to optic radiations and visual cortex regions where early changes can parallel motor-related pathophysiology [56–59].

Diffusion Kurtosis Imaging (DKI), another advanced diffusion MRI technique, quantifies the non-Gaussian behavior of water diffusion, enabling more detailed characterization of tissue complexity and heterogeneity [60]. DKI provides metrics such as mean kurtosis (MK), which reflect microstructural complexity and can capture subtle tissue changes not visible through conventional diffusion metrics. In Alzheimer's and Parkinson's diseases, DKI has identified early gray matter changes, such as those in the hippocampus or cortical regions, and its sensitivity has similarly been extended to white matter pathways critical for sensory and integrative processing [61–63]. The ability of DKI to detect preclinical tissue changes makes it a potential biomarker for monitoring both neural and peripheral axonal integrity.

AI models, particularly machine learning techniques such as random forest classifiers, have been instrumental in leveraging the multidimensional data generated by NODDI and DKI for enhanced diagnostic precision [64]. By integrating neurite density and dispersion metrics with kurtosis-derived features, these algorithms can identify subtle patterns of pathology across brain regions and visual sensory pathways. For instance, studies training models on multimodal diffusion data have achieved up to 94% classification accuracy in distinguishing early-stage Alzheimer's from healthy controls [65]. Such applications underscore the potential of these imaging modalities when paired with AI to dissect intricate, region-specific changes in diseases with diffuse pathophysiology. The fusion of these advanced techniques highlights their promise in enabling earlier intervention and in offering mechanistic insights into diseases affecting both central and peripheral nervous systems, including the optic nerve and its connections [66].

II. Next-Generation Positron Emission Tomography (PET) Tracers

Positron Emission Tomography (PET) has remained a cornerstone of molecular neuroimaging, offering unparalleled ability to visualize and quantify the in vivo accumulation of pathological proteins central to neurodegenerative and inflammatory processes [67]. The advent of next-generation PET tracers has markedly enhanced the sensitivity and specificity of PET imaging,

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particularly in disorders characterized by the aggregation of misfolded proteins such as tau, amyloid-beta, and alpha-synuclein, as well as in conditions marked by neuroinflammatory activity [68,69].

Second-generation tau PET tracers, including 18F-PI-2620 and 18F-MK-6240, have demonstrated superior binding selectivity compared to their predecessors, enabling more accurate quantification of tau pathology [70–72]. Tau PET imaging has proven instrumental not only in diagnosing Alzheimer's disease but also in distinguishing tauopathies from other forms of dementia with sensitivities and specificities exceeding 90% [73–75]. The precision of these tracers has implications for detecting subtle tau-related changes, including those within the visual pathways, where tau pathology can manifest in early neurodegenerative or ocular-related conditions. These high-fidelity tracers provide insights into disease progression, particularly when tau pathology begins to affect structures like the visual cortex or optic radiations, enabling earlier intervention [76–78].

For synucleinopathies, such as Parkinson's disease and Lewy body dementia, the development of PET tracers targeting α-synuclein aggregates represents a groundbreaking advancement [79–81]. Although still under clinical evaluation, tracers like 11C-MODAG-001 have shown promise in preclinical studies, with the potential to visualize synuclein deposits in regions critical to motor and sensory processing, including structures implicated in visual-motor integration [82,83]. These advancements could pave the way for pre-symptomatic detection of α-synucleinopathies, broadening the applicability of PET imaging to conditions where early sensory or visual deficits emerge [84–86].

AI-driven analysis tools, particularly deep learning algorithms, are further enhancing the diagnostic utility of PET imaging by automating and refining image interpretation [87–89]. Convolutional neural networks (CNNs), including advanced 3D CNN architectures, have been effectively applied to PET datasets, achieving diagnostic accuracies that rival expert interpretation. For example, AI models analyzing 18F-flortaucipir PET scans for Alzheimer's detection have reported diagnostic accuracy rates as high as 98.8% [90–94]. These technologies can also facilitate the integration of PET data with structural and diffusion imaging modalities, creating multimodal frameworks capable of capturing early changes in both cortical and subcortical structures, including those relevant to visual processing.

By automating PET scan analysis, AI significantly reduces the reliance on manual interpretation, accelerating clinical workflows and enabling more widespread adoption of PET imaging [95–97]. This is particularly relevant for conditions where dynamic or multimodal imaging is required to monitor disease progression or response to targeted therapies. The integration of PET imaging with advanced AI systems holds tremendous potential for unraveling complex pathologies that affect interconnected brain and sensory systems, enabling personalized diagnostic and therapeutic approaches.

III. Multi-Modal Integration

One of the most transformative advancements in the application of AI to neuroimaging is its ability to integrate data from multiple imaging modalities—such as structural MRI, functional MRI (fMRI), PET, and genetic data—into unified diagnostic frameworks [98,99]. This multimodal approach provides a comprehensive understanding of diseases that affect interconnected systems, such as neurodegenerative and neuro-ophthalmic disorders, by capturing structural, functional, and molecular insights that single-modality imaging often misses [100,101]. For example, in diseases like MS, NMO, and MOG antibody disease, where the visual system is frequently involved, such integration enables the detection of both central and peripheral pathology. Transformer-based AI models, such as the Vision Transformer (ViT), have demonstrated remarkable utility in processing multimodal neuroimaging data [102,103]. Initially designed for natural language processing, ViT has been successfully adapted for 3D medical imaging, enabling it to capture long-range dependencies within neural and visual structures [104]. For instance, a study using 3D ViT models to classify Alzheimer's disease from healthy controls achieved an accuracy of 96.7%, outperforming traditional CNN-based models [105]. Extending these capabilities to neuro-ophthalmic contexts, ViT models can analyze the optic radiations, lateral geniculate nucleus (LGN), and visual cortex, detecting subtle alterations associated with early inflammatory or degenerative changes.

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Multimodal Transformer networks, such as the Multimodal Transformer for Alzheimer's Disease (MT-AD), similarly exemplify the power of integrating diverse datasets. The MT-AD framework fuses data from structural MRI, fMRI, PET imaging, and genetic profiles, achieving a remarkable area under the receiver operating characteristic curve (AUC) of 0.98 in early Alzheimer's detection [106,107]. In neuro-ophthalmic disorders, this integration could detect disruptions in the visual pathway, including optic nerve damage (as seen in MS, NMO, and MOG antibody disease) or cortical involvement in the visual cortex, which may precede overt clinical symptoms. By capturing cross-modal patterns of structural degeneration and metabolic changes, AI systems can identify early biomarkers in both the brain and the visual system [108–110].

Graph Neural Networks (GNNs) further enhance multimodal analysis by modeling connectivity patterns across brain networks [111,112]. The Brain Connectivity Graph Neural Network (BC-GNN) integrates data from MRI, PET, and diffusion tensor imaging (DTI) to map functional and structural networks with exceptional precision [113]. For example, BC-GNN has been shown to distinguish early-stage Parkinson's disease from healthy controls with an accuracy of 92% [114,115]. When applied to neuro-ophthalmic diseases, GNNs could reveal disruptions in connectivity between the visual cortex, LGN, and other sensory processing regions. This approach enables the identification of subtle connectivity changes that traditional imaging methods might miss, particularly in diseases where the visual system serves as a critical early indicator of broader neurological dysfunction.

The integration of multimodal imaging, driven by AI, holds significant potential for transforming the diagnosis and management of neuro-ophthalmic disorders. For example, in MS, the combination of structural MRI to assess optic nerve integrity, fMRI to evaluate visual cortex activity, and PET to detect inflammatory markers along the visual pathway provides a unified framework for understanding disease progression. These multimodal approaches not only improve diagnostic accuracy but also offer novel insights into the interplay between central and peripheral systems, enabling earlier and more personalized interventions.

IV. Translational Impact

The clinical translation of these advanced neuroimaging and AI technologies is rapidly advancing, with significant implications for the diagnosis, prognosis, and treatment of neurodegenerative diseases [116,117]. The integration of AI-driven systems with neuroimaging has the potential to revolutionize not only early detection but also personalized medicine in neurology, offering a more tailored and effective approach to patient care [118,119]. One notable example of translational research is the development of adaptive deep brain stimulation (DBS) systems for Parkinson's disease [120,121]. Traditional DBS therapy uses a fixed stimulation pattern, which can provide symptomatic relief but does not account for the dynamic nature of the disease [122]. Adaptive DBS systems leverage real-time feedback from neuroimaging and AI algorithms to adjust stimulation parameters based on the patient's current brain state [123,124]. By continuously monitoring brain activity and adjusting the stimulation in real-time, these systems can optimize therapeutic effects, improving motor function while reducing side effects such as dyskinesia [125,126]. Some studies have reported up to a 30% improvement in motor symptoms when using adaptive DBS systems compared to conventional methods [127]. AI-enhanced retinal imaging is another area where significant advancements are being made in the non-invasive detection of neurodegenerative diseases [128,129]. Optical coherence tomography (OCT) imaging of the retina has gained traction as a low-cost, easily accessible method for identifying early neurodegenerative changes [130,131]. Machine learning algorithms trained on OCT images can detect subtle changes in retinal morphology that correlate with brain pathology, offering a potential diagnostic tool for early-stage disease detection [132,133]. Studies have reported sensitivities and specificities exceeding 90% for detecting early-stage Alzheimer's disease (AD) and Parkinson's disease (PD) using AI models applied to OCT data [134,135].

V. Privacy and Data-Sharing

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Further advancements in federated learning have the potential to address the privacy and data-sharing challenges inherent in medical research, particularly in neuroimaging studies [136,137]. Federated learning enables AI models to be trained on decentralized datasets across multiple institutions without the need to centralize sensitive patient data [138]. This approach could accelerate the development of AI-driven diagnostic tools by providing access to larger, more diverse datasets while maintaining patient privacy [139,140]. Federated learning has already shown promise in enabling collaborative research across medical institutions and could be particularly valuable for creating AI models capable of generalizing across diverse populations and clinical settings [141,142]. Another emerging frontier is the integration of neuroimaging biomarkers with liquid biopsy techniques, such as blood-based assays for amyloid-β, tau, and other neurodegenerative proteins [143,144]. Combining neuroimaging data with molecular markers from blood samples could provide a more comprehensive, non-invasive method for diagnosing and tracking disease progression [145,146]. AI models could be used to integrate these data streams, enhancing their predictive power and enabling a more personalized approach to monitoring disease progression [147,148]. Early detection through blood biomarkers, combined with neuroimaging, holds great potential for detecting diseases like Alzheimer's and Parkinson's in their pre-symptomatic stages, allowing for earlier interventions that may slow disease progression [149,150].

The integration of AI-driven multimodal imaging systems with advanced neurophysiological monitoring also opens up new possibilities for the real-time assessment of brain function in clinical settings [151,152]. For example, coupling structural and functional MRI with electrophysiological data from techniques such as electroencephalography (EEG) or magnetoencephalography (MEG) could provide real-time insights into brain activity and connectivity [153,154]. AI models trained on these multimodal data could detect changes in brain networks that precede clinical symptoms, allowing for early intervention and potentially slowing the onset of neurodegenerative diseases [155,156].

VI. Impact on Neurorehabilitation

Beyond diagnosis and monitoring, these technologies also have great potential to transform neurorehabilitation. For example, functional MRI (fMRI) can be used to track changes in brain activity as patients engage in rehabilitative tasks [157–159]. When combined with real-time AI analysis, fMRI data could guide adaptive neurorehabilitation strategies, providing personalized feedback to patients and clinicians to enhance recovery [160,161]. Similarly, AI-driven analysis of diffusion MRI could identify regions of the brain that are most vulnerable to neurodegeneration, allowing for targeted rehabilitative interventions aimed at preserving brain function [162,163]. Further, while transcranial stimulation, including techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has shown promise in modulating brain activity, its application in AI-directed neurostimulation remains an emerging field [164,165]. Current studies focus on using AI to optimize stimulation parameters, but direct evidence supporting its clinical efficacy in neurodegenerative diseases is limited. Further research is needed to validate these methods in controlled settings before widespread adoption [167,168].

Table 1. Summary of Key Neuroimaging Techniques and AI Integration in Clinical Practice for Disease Diagnosis and Treatment.

Technology	Details
Diffusion Tensor Imaging (DTI)	Provides insights into white matter integrity, useful for detecting disease progression in neurodegenerative diseases. However, limited in differentiating microstructural changes in tissue.
Neurite Orientation Dispersion and	Enhances the detection of early microstructural changes in diseases like Parkinson's. Offers more nuanced views of white matter integrity. Requires specialized equipment and computational power.

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Density Imaging (NODDI)	
Diffusion Kurtosis Imaging (DKI)	Detects non-Gaussian diffusion behavior and identifies early gray matter changes in diseases such as Alzheimer's. Clinically relevant but requires sophisticated analysis tools.
AI Integration with NODDI and DKI	AI improves diagnostic accuracy by analyzing complex data, enabling early detection with higher precision (e.g., 94% accuracy for Alzheimer's detection). Models require continuous validation.
Tau PET Tracers (e.g., 18F-PI-2620)	Enhances specificity and sensitivity for tau imaging, crucial for early Alzheimer's diagnosis. Challenges include availability and cost.
Alpha-Synuclein PET Tracers (e.g., 11C-MODAG-001)	Key for diagnosing synucleinopathies like Parkinson's at earlier stages. Still in clinical trials, but offers the potential to detect disease before symptoms appear.
AI-driven PET Imaging (CNNs, 3D CNN Architectures)	AI systems automate PET scan analysis, reducing manual interpretation time and improving diagnostic consistency. Requires transparency for trust and clinical integration.
Transformer-based AI Models (e.g., Vision Transformer)	AI models like ViT capture long-range dependencies in 3D data, improving diagnostic accuracy for conditions like Alzheimer's. Need for large, high-quality datasets and computational resources.
Graph Neural Networks (GNNs) for Brain Connectivity	GNNs model brain connectivity disruptions, critical for early-stage Parkinson's diagnosis. Requires high data consistency and overcoming complex integration barriers.
Adaptive Deep Brain Stimulation (DBS)	AI enhances DBS by adjusting stimulation in real time, improving therapeutic outcomes for Parkinson's patients. Challenges include regulatory approval and monitoring for continuous adaptation.
AI-enhanced Retinal Imaging (Optical Coherence Tomography - OCT)	Provides a non-invasive, cost-effective method for detecting early-stage Alzheimer's and Parkinson's by identifying retinal changes linked to brain pathology. Still not universally adopted.
Neuroimaging Biomarkers + Liquid Biopsy	Combining neuroimaging with blood biomarkers offers a comprehensive, non-invasive approach for monitoring disease

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	progression and enabling early interventions. Requires data integration strategies.

Challenges in Integrating AI into Clinical Practice for Diagnosis and Treatment

The application of AI faces significant technical challenges, primarily due to the inherent variability of neuroimaging data [169–174]. This variability stems from multiple sources, creating a complex landscape that impacts AI model accuracy and generalizability [175]. Variability across MRI scanners, imaging protocols, and patient positioning introduces inconsistencies that must be addressed for AI models to function reliably across diverse clinical settings.

I. Technical Challenges: Variability in Neuroimaging Data and Its Impact on AI Models

Scanner variability is one such challenge. Even MRI scanners from the same manufacturer can produce slightly different image characteristics, such as differences in field strength (e.g., 1.5T vs. 3T), gradient performance, radiofrequency coil designs, and reconstruction algorithms [207]. These variations can lead to inconsistencies in image contrast, resolution, and signal-to-noise ratio, which may confound AI algorithms trained on data from specific scanner types [208].

Protocol variability also poses a challenge. Imaging protocols can vary significantly between institutions and even within the same institution over time. Differences in pulse sequences, acquisition parameters (such as repetition time [TR], echo time [TE], and flip angle), contrast agent usage, and image plane orientation contribute to disparities in tissue contrasts and artifact patterns [209]. These variations can negatively impact the generalizability of AI models, which may be trained on data from specific protocols but then need to perform effectively across a range of imaging settings [210].

Patient positioning and motion during scans further complicate the issue. Variations in head orientation, motion artifacts, and physiological noise (such as respiratory and cardiac cycles) introduce distortions and misalignments in images, which can affect AI model performance [211,212]. In clinical settings, such variability is inevitable, and AI models must be capable of mitigating its effects to maintain diagnostic accuracy.

Another source of variability arises in image preprocessing. Different preprocessing pipelines used to prepare neuroimaging data for analysis can introduce inconsistencies in the final images. Techniques such as bias field correction, skull stripping, registration, normalization, and intensity standardization can all vary, potentially affecting AI model performance if not consistently applied [213,214].

Longitudinal changes present additional challenges in studies tracking disease progression over time. Factors such as scanner upgrades, protocol updates, or patient-specific changes unrelated to the disease being studied can introduce confounding variables that AI models must account for in order to accurately track disease progression [215].

Finally, multi-site data integration introduces complexities that AI models must overcome to ensure their robustness. Data from different sites can differ in terms of patient demographics, clinical assessment protocols, and data quality control measures. Such site-specific biases can hinder the generalizability of AI models, necessitating careful strategies to ensure that models are effective across diverse clinical environments [216,217].

II. Regulatory and Legal Barriers: Ensuring Compliance and Addressing Liability

These technical challenges directly tie into regulatory concerns. The U.S. Food and Drug Administration (FDA) requires substantial evidence that AI-based diagnostic devices maintain performance across diverse conditions, including variations in scanner types, protocols, and patient populations [176,177]. This requirement poses significant hurdles for AI developers, as they must demonstrate the ability of their models to remain reliable and accurate across different clinical settings. The FDA requires AI models to be validated under regulatory pathways such as the 510(k) pathway or Premarket Approval (PMA) processes [179]. For example, AI models must be robust to

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scanner variability, requiring validation studies using data from multiple scanner models and manufacturers to ensure consistent performance [218]. Similarly, AI models must be able to handle protocol variability, potentially requiring the development of protocol-agnostic architectures or extensive fine-tuning capabilities to maintain performance across different imaging protocols [219]. AI systems may also need to demonstrate resilience to motion artifacts, possibly requiring the integration of motion correction algorithms or the ability to flag highly motion-corrupted images for manual review [220]. Furthermore, the FDA may mandate preprocessing standardization or require models to be robust to variations in preprocessing methods, which could drive the development of industry-wide standards for neuroimaging AI applications [221]. For AI systems designed to track disease progression, the FDA may require evidence of longitudinal consistency, ensuring that the model performs effectively despite scanner upgrades, protocol changes, or other temporal variations [222]. Lastly, the FDA is likely to require validation of AI model performance across multiple sites and diverse patient populations to ensure multi-site generalizability, which may involve extensive multi-center validation studies [223].

Liability for misdiagnosis due to image variability is also a primary concern. If an AI system misdiagnoses a patient because of such variability, questions about responsibility arise. Determining liability—whether it lies with the AI developer, healthcare provider, or imaging facility—may require new legal frameworks to address AI-assisted diagnoses [224]. Additionally, data sharing and privacy are critical concerns. Sharing medical imaging data across institutions is necessary to develop robust AI models, but it raises privacy issues and must comply with regulations like HIPAA in the United States and GDPR in the European Union. This creates a tension between the need for diverse training datasets and the protection of patient privacy rights [225]. Informed consent also becomes a crucial issue. Patients must be informed that AI systems are being used in their diagnosis, including the potential for errors due to variability in the data. Communicating the risks and benefits of AI-assisted diagnosis to patients is a legal challenge in itself [226]. Furthermore, existing FDA regulatory approval pathways, such as the 510(k) and PMA processes, may not be well-suited to the unique characteristics of AI systems that continuously learn and adapt. New regulatory frameworks may be necessary to address these concerns [227]. Post-market surveillance is another area where traditional methods may be inadequate. AI systems that evolve over time must be monitored to ensure they do not introduce new risks or errors, which may require new approaches to post-market monitoring and regulation [228]. Finally, international harmonization of regulations becomes increasingly important as AI systems are deployed globally. Different regulations across countries regarding medical AI and data privacy could complicate the widespread adoption of AI tools, necessitating efforts toward international regulatory alignment [229].

III. Future Directions: Addressing Variability Through AI Innovations

Several potential solutions and future directions are being explored to address these challenges. Adaptive neuroimaging harmonization (ANH), utilizing transfer learning and domain adaptation, shows promise in mitigating issues related to scanner and protocol variability, although regulatory concerns remain regarding how these adaptive techniques fit into current frameworks [181,182]. Federated learning is another promising approach, allowing AI models to be trained on distributed datasets without centralizing sensitive patient data, thus addressing privacy concerns while maintaining access to diverse training data [230]. The development of explainable AI models is crucial for improving transparency and addressing liability concerns, as clinicians need to understand and validate AI-generated diagnoses [231]. Industry-wide standardization efforts aimed at creating uniform neuroimaging protocols and preprocessing pipelines could help reduce variability and improve model generalizability [232]. Synthetic data generation techniques, which generate realistic and diverse datasets, can help augment training datasets and enhance the robustness of AI models. Similarly, the development of continuous learning frameworks could help safely integrate adaptive AI systems that evolve over time, ensuring that AI tools remain accurate and reliable in clinical practice [233].

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Table 2. Main challenges clinicians face when integrating AI technologies into diagnosis and treatment.

Challenge	Details
Variability in Imaging Data	Variations in MRI scanners, protocols, patient positioning, and preprocessing pipelines create inconsistencies that impact the accuracy and generalizability of AI models. This affects their performance across diverse clinical settings.
Scanner and Protocol Differences	Even within the same manufacturer, MRI scanners may produce different image characteristics (e.g., field strength, coil design), leading to variability in diagnostic accuracy. Variability in imaging protocols across institutions further complicates AI's ability to generalize and maintain consistent performance.
Patient Positioning and Motion	Variations in patient positioning and involuntary motion (e.g., respiratory, cardiac cycles) introduce distortions that can negatively affect AI-driven diagnoses. AI models must account for such variability in real-time to maintain diagnostic accuracy.
Image Preprocessing Variability	Differences in preprocessing steps (e.g., skull stripping, registration, normalization) can lead to inconsistencies in the final image data, potentially hindering AI performance if not standardized across clinical settings.
Longitudinal Variability	Changes in imaging technology, protocols, and patient-specific factors over time complicate longitudinal tracking of disease progression. AI models must adapt to these changes to remain effective in monitoring disease development.
Multi-Site Data Integration	Data from different clinical sites can vary due to differences in patient demographics, protocols, and quality control measures. AI models must be robust enough to handle these variations to ensure they work across a wide range of clinical environments.
Regulatory Compliance	The FDA requires rigorous validation of AI models to ensure they perform reliably across diverse clinical conditions. Models must be validated under appropriate regulatory pathways, such as 510(k) or PMA, while also adapting to evolving scanner technology and clinical protocols.
Legal Liability	AI-driven misdiagnosis due to image variability raises liability questions about who is responsible (AI developer, healthcare provider, or imaging facility). New legal frameworks may be needed to clarify liability for AI-assisted diagnoses.
Data Privacy and Security	Sharing medical imaging data across institutions is essential for developing robust AI models, but it raises concerns over patient privacy. Adhering to HIPAA, GDPR, and other data protection regulations creates tension between the need for diverse training data and safeguarding privacy.
Informed Consent	Patients must be informed about the role of AI in their diagnosis and the potential risks of errors due to data variability. Clearly communicating the benefits and limitations of AI-assisted diagnoses is a critical ethical and legal issue.

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Regulatory Gaps for AI Adaptation	Current FDA regulatory pathways may not fully accommodate the continuous learning nature of AI systems, raising the need for new regulatory frameworks to address the evolving nature of AI models.
Post-Market Surveillance	AI systems that adapt over time require continuous monitoring to ensure they do not introduce new risks or errors. Traditional post-market surveillance methods may not be suitable for AI's dynamic nature, necessitating the development of new approaches.
International Regulatory Alignment	Different regulations regarding medical AI and data privacy across countries complicate global adoption. Efforts toward international regulatory harmonization are necessary to facilitate widespread deployment and ensure patient safety.

Discussion

The convergence of advanced neuroimaging and artificial intelligence (AI) in the diagnosis and treatment of neurodegenerative diseases has the potential to significantly alter the clinical landscape. However, while the promise of these technologies is vast, their integration into routine clinical practice presents both opportunities and challenges that require careful consideration.

At the heart of this transformation is the ability to detect subtle, early changes in the brain that were previously undetectable. Advanced imaging techniques like diffusion MRI (e.g., NODDI and DKI) offer clinicians a powerful tool to observe microstructural alterations before cognitive or motor symptoms appear. Early detection could mean that interventions are started at a point where they are more effective, potentially delaying disease progression or improving quality of life. This shift from reactive to proactive healthcare is a paradigm shift that clinicians can take advantage of, allowing for more targeted, timely interventions. The real challenge for clinicians, however, is in translating these early imaging findings into actionable clinical decisions.

The real-world application of these technologies goes beyond simply diagnosing disease earlier; it's about enhancing the precision and personalization of treatment. Imagine a scenario where a clinician is able to combine advanced neuroimaging findings with AI-driven insights to not only detect the disease but also predict its trajectory based on individual brain structure and function. AI tools can help clinicians identify the subtle distinctions in disease progression that might otherwise go unnoticed, allowing for more personalized therapeutic approaches. For example, AI-enhanced models could suggest whether a patient with early Alzheimer's is likely to experience rapid cognitive decline or whether their disease might remain relatively stable for an extended period. This level of precision allows for more informed treatment plans and the ability to tailor interventions to each patient's unique presentation, ensuring that patients receive the most appropriate care based on their specific needs.

While the potential for personalized care is tremendous, the integration of these advanced technologies into clinical practice is not without its challenges. One of the most significant hurdles is ensuring that clinicians can trust and understand the outputs of AI models. AI systems excel at processing complex data and detecting patterns, but the clinical decision-making process requires context—an understanding of the patient's full medical history, symptoms, and personal circumstances. AI can provide invaluable insights, but clinicians must remain at the forefront of the decision-making process, using AI as a tool to augment their expertise, not replace it. The integration of AI into clinical practice should not lead to a dehumanization of care, where patients become data points in a system, but rather should enhance the clinician's ability to make well-informed, empathetic decisions.

Moreover, the successful use of AI and neuroimaging in clinical practice requires clinicians to have the appropriate training and support. AI systems are powerful, but they are only as effective as the people using them. The current medical education system, which primarily trains clinicians in traditional methods of diagnosis and treatment, must evolve to ensure that healthcare providers are equipped with the skills to work alongside advanced AI technologies. This could mean more

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emphasis on data literacy, AI ethics, and the interpretation of complex neuroimaging data as part of medical training. Additionally, clinicians must have the infrastructure and tools necessary to integrate these technologies into their daily workflows. This includes having access to AI-driven diagnostic tools, real-time neuroimaging feedback, and seamless systems for managing and interpreting multimodal data.

Another key consideration is the ethical and regulatory landscape. The widespread use of AI in healthcare raises questions about data privacy, algorithmic bias, and accountability. Who is responsible if an AI system makes an error in diagnosis or treatment? What safeguards are in place to protect patient data when it is processed by machine learning models? These are critical questions that clinicians must be prepared to answer as they begin to incorporate AI into their practice. Furthermore, as AI models are continuously trained on new data, they may evolve in ways that are not immediately predictable. This raises concerns about the long-term reliability and consistency of AI systems. Clinicians need to feel confident that the systems they rely on are safe, transparent, and governed by ethical principles that prioritize patient welfare.

Looking to the future, the combination of AI and advanced neuroimaging offers a vision of personalized medicine that was once unimaginable. It holds the potential to revolutionize not only how we diagnose and treat neurodegenerative diseases, but also how we think about patient care as a whole. The ability to tailor treatments to individual patients, predict disease progression, and intervene at earlier stages could significantly alter the course of neurodegenerative diseases. However, for this vision to be realized, the healthcare system must prioritize collaboration between clinicians, researchers, and AI developers. Only through this collaborative effort can we ensure that these technologies are implemented in ways that enhance, rather than disrupt, the patient care experience.

Ultimately, the success of integrating AI and advanced neuroimaging into clinical practice hinges on a balanced approach—one that combines technological innovation with clinical expertise, ethical oversight, and patient-centered care. By embracing these tools thoughtfully and carefully, clinicians can not only improve diagnostic accuracy and treatment outcomes but also pave the way for a new era of personalized, data-driven healthcare.

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