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Exploring Longitudinal MRI-Based Deep Learning Analysis in Parkinson's Patients - A Short Survey Focus on Handedness

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ABSTRACT

Parkinson's Disease (PD) is a prevalent progressive neurodegenerative condition affecting millions globally. Research has found that individuals with PD have a reduced risk of certain cancers, such as colon, lung, and rectal cancers, but an increased risk of brain cancer. Therefore, there is an urgent need for the development of advanced PD diagnostic methods and for investigating the relationships between risk factors, such as lifestyle due to handedness associated with various types of cancers. Recent ad- vancements in magnetic resonance imaging have enhanced PD diagnosis, reducing misdiagnosis and facilitating more accurate disease progression monitoring. Nevertheless, challenges exist, particularly in the distinction of PD between left-handed and right-handed patients over time. This survey provides an overview of contemporary deep learning-based imaging analysis methodologies, encompassing both non-longitudinal and longitudinal contexts. We also explore existing limitations and prospects for refinement to gain deeper insights. These insights are poised to inform the development of personalized treatment strategies for PD patients while elucidating the current disparities between deep learning models and their efficacious implementation in clinical practice.

KEYWORDS

Parkinson's Disease; PD; deep learning; UNet, Handedness

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1. Introduction

Parkinson's Disease (PD) is a persistent and incapacitating neurodegenerative disease that impacts millions of people globally. It ranks as the second most prevalent neurodegenerative disorder, following Alzheimer's disease [1]. It is primarily characterized by the degeneration of striatal dopaminergic neurons in the substantia nigra, resulting in motor symptoms such as bradykinesia, tremors, and rigidity [2]. Additionally, non-motor symptoms may arise due to the en- gagement of other neurotransmitter systems, contributing to neuronal loss in non-dopaminergic regions and there can be overlap between motor and non- motor symptoms. This disease exerts a substantial clinical impact on patients, particularly in the age group of those over 65, which comprises the largest number of PD patients [3]. It profoundly affects patients, their families, and caregivers due to its progressive degenerative impact on mobility and muscle control. Furthermore, prior research has established a connection between the development of cancer subsequent to a PD diagnosis. Several studies have revealed a positive correlation between PD and melanoma and brain cancers, while others have identified a negative association between PD and colon, rectal, colorectal, and lung cancers [4]. Therefore, it is imperative to delve deeper into the role of certain risk factors, such as lifestyle habits influenced by handedness, genetic variants, gender, etc. in influencing the subsequent cancer risk among PD patients [4–10].

Neuroimaging plays a major role in supporting the clinical diagnosis of PD by differentiation of PD from other diseases or atypical Parkinsonism. Recent advancements in Magnetic Resonance Imaging (MRI) have significantly enhanced PD diagnostic accuracy, reduced the incidence of misdiagnosis, streamlined early detection, and hold promise for effectively tracking and monitoring disease progression [11, 12]. Many different MRI techniques are being employed in PD research and diagnosis including structural MRI, Functional MRI (fMRI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and Quantitative Susceptibility Mapping (QSM), etc [13]. Indeed, the different MRI techniques offer distinct approaches and advantages when diagnosing and studying different brain regions of the nervous system and different types of neurons in PD. The selection of the most suitable MRI technique and magnetic field strength frequently hinges on the specific research question and the particular region of interest. By amalgamating diverse MRI methodologies, researchers can attain a more all-encompassing comprehension of the disease's underlying mechanisms, encompassing its effects on diverse cerebral regions and intricate neural models [14, 15].

Nonetheless, various factors have impeded progress in the field of MRI-based PD diagnosis, including relatively high cost, while the more significant bottleneck in MRI utilization stems from the shortage of radiology specialists capable of interpreting the images and synthesizing the information to establish a diagnosis [15]. Another limitation is that, for certain specific research questions, there remains a shortage of comprehensive and efficient approaches for diagnosis and imaging analysis. For example, the role of handedness in disease manifestation and progression remains a relatively unexplored area.

Handedness, the preference for using one hand over the other for most activities, is a fundamental aspect of human neurobiology. Approximately 90% of the population is right-handed, while the remaining 10% are either left-handed or ambidextrous [16]. Studies have shown that there are differences in brain activity loss between patients with different dominant hand preferences in PD and found that the genetic variants contribute to neurodevelopmental lateralization of brain organization, which in turn influences both the handedness phenotype and the predisposition to develop certain neurological and psychiatric diseases based on genotypes and brain image scans of about 9,000 participants from more than 400,000 people ages from 40 to 69 selected from the UK Biobank [17, 18]. Our previous study also has demonstrated a significant difference in step counts, which serve as an important means of quantifying declining ambulatory behavior associated with disease progression, between right-handed versus left-handled or ambidextrous PD patients [19]. Handedness's potential influence on PD has only recently gained attention and as of the most recent data available, there is limited research and a scarcity of relevant

papers on the subject.

Our review aims to bridge this gap by offering an exploration of current imaging analysis techniques [20–25] used in PD research. We specifically emphasize a modeling perspective, encompassing deep learning (DL), one subfield of artificial intelligence (AI) techniques, made feasible by the current advancements in computing power and more availability of large datasets. Additionally, we emphasize the differentiation between right-handed and left-handed patients. By doing so, we hope to uncover valuable insights that can inform personalized treatment strategies for PD patients and highlight current gaps between the AI automation models and their effective implementation in the final clinical setting.

2. MRI imaging sequences in PD patients

A recent study [18] has confirmed that left-handers, who possess a gene associated with improved verbal skills, have a lower risk of PD when compared to right-handers. This study revealed an increase in measures of spontaneous temporal synchronization (functional connectivity) between left and right language models in left-handers and the cytoskeletal differences associated with handed- ness are observable in the brain. Verreyt N et al [17] wrote a review paper and also concluded the differences in cognitive performance. Left-handed PDs exhibit weaker performance in spatial attention, visuospatial orienting, and mental imagery tasks while better in language tasks. It's important to note that PD patients don't necessarily exhibit a uniform cognitive profile. Instead, symptom laterality, or the side of the brain affected, is a crucial factor that must be considered. Inspired by those discoveries, we foresee that conducting imaging analyses comparing left-handed and right-handed PD patients could offer a promising avenue for a more profound understanding. It also presents a viable path to assist radiologists in achieving automated and efficient disease diagnoses by harnessing the capabilities of advanced MRI imaging analysis.

MRI's non-invasive nature has been a revolutionary tool in neurology, particularly in diagnosing and differentiating movement disorders like PD from its mimics [26]. Leveraging its non-invasive nature and high-resolution capabilities, MRI provides profound insights into the structural and functional aberrations inherent to PD. These insights span from elucidating the pathophysiological hallmarks, such as iron accumulation in the substantia nigra [27], to mapping intricate neural connectivity patterns disrupted by the disease [28]. Furthermore, MRI's aptitude in differentiating PD from other atypical parkinsonian syndromes bolsters its diagnostic and prognostic value, ensuring tailored therapeutic approaches [26]. As research endeavors continue to expand, MRI remains at the forefront, offering a panoramic window into the neural underpinnings and disease progression of PD, shaping the future trajectory of both clinical practice and scientific exploration [29].

Two basic MR images are T1-weighted (T1) and T2-weighted (T2) sequences, which are shown in Figure 1. A third commonly used sequence-the Fluid Attenuated Inversion Recovery (FLAIR) has been introduced as a complement of, or even a replacement for the T2. The visual assessment of T1 and T2 is normal in patients with early PD but provides a main role of detecting or ruling out other underlying pathologies causing PD [30].

T1-weighted images play a pivotal role in a range of analyses related to brain atrophy, encompassing measurements of diameter, area, and volumes [31]. These analyses are typically integral to automated volume assessments, aiding in the quantification of structural changes in the brain over time. Such analyses are fundamental for gaining insights into brain health and facilitating the diagnosis of neurological conditions [32]. Atrophy patterns are better demonstrated by T1-weighted images, displaying anatomical details and providing an excellent grey and white matter contrast. More recently, advanced T1 sequences were developed to improve the detection of nigral changes in PD patients. These include a variety of inversion recovery images [33–36] and a recently developed neuromelanin-sensitive T1-weighted sequence [37–39].

On the other hand, T2 and FLAIR images exhibit heightened sensitivity to alterations in tissue properties and

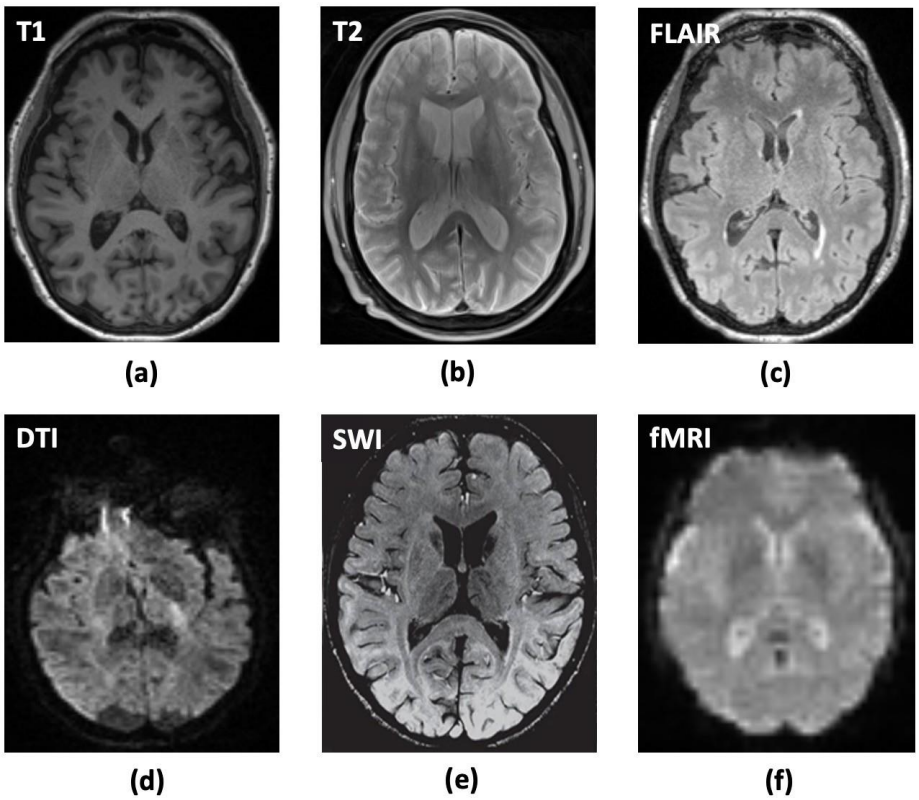

Figure 1. Illustration magnetic resonance imaging.

Notes: (a) T1-weighted MR images, (b) T2-weighted MR images, (c) FLAIR sequences-based MR im- ages), (d) diffusion tensor imaging (DTI), (e) susceptibility-weighted imaging (SWI) and (f) functional MRI (fMRI) characteristics of Parkinson's disease patients.

are frequently employed to identify abnormalities, pinpoint fluid accumulations, and evaluate soft tissue characteristics. An elevated T2-weighted signal in MRI scans typically indicates issues like de- generation, demyelination, or gliosis in the white matter regions of the brain. Conversely, a reduced T2-weighted signal is usually observed in the subcortical grey matter nuclei, which could suggest the accumulation of paramagnetic substances, like iron. To enhance the detection of such iron deposits, techniques like T2-weighted gradient echo or susceptibility-weighted imaging sequences can be utilized. These methods are especially sensitive to magnetic susceptibility effects caused by iron. Furthermore, higher magnetic field strengths in MRI, such as those found in more advanced MRI machines, can provide greater spatial resolution. This increased resolution may lead to a more precise measurement of iron accumulation in specific subcortical regions, like the substantia nigra (SN) and striatum. This precision is particularly useful in distinguishing different types of neurodegenerative disorders that affect movement, such as Parkinson's. One example of T1 and FLAIR MRI images on right and left-handed Parkinson patients is shown in Figure 2. Thanks to the advancements in T1 and T2 weighted MRI brain imaging sequences, AI-based models for automated imaging diagnosis and segmentation based on those imaging sequences have emerged as invaluable tools within the realm of medical imaging.

The evolution of MRI modalities has engendered a paradigm shift in the diagnostic landscape of PD. Chief among these innovations are Diffusion-Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), and the increasingly recognized Susceptibility Weighted Imaging (SWI). According to [40], DWI and DTI, by delineating the microscopic motion of water molecules, offer unparalleled in- sights into the integrity of white matter. Crucially, these techniques have been instrumental in identifying micro-structural deviations within the substantia ni-gra, a region unequivocally implicated in PD's pathophysiology [41]. SWI, on the other hand, is noted for its acute

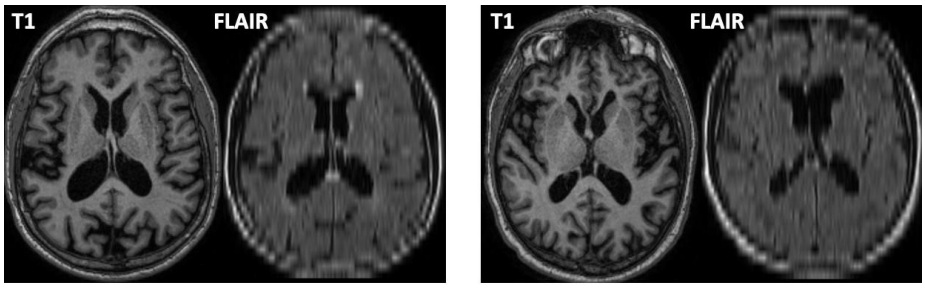

Figure 2. Illustration magnetic resonance imaging (include T1 and FLAIR weights) on left and right-handed Parkinson's patients.

Notes:(a) presents the images from right-handed Parkinson's patients; (b) presents the images from left- handed Parkinson's patients.

sensitivity to magnetic susceptibilities, notably iron. [42] highlight that the discernable iron accumulation, particularly in the substantia nigra, is emblematic of PD. Furthermore, this iron buildup has potential implications for PD severity, with emerging evidence suggesting a correlation between heightened iron levels and more advanced disease stages. Parallelly, Functional MRI (fMRI) has solidified its status as an indispensable investigative tool. [43] emphasized that fMRI's capability to monitor cerebral hemodynamics allows for a granular examination of neural models and connectivity patterns-key players in PD's neurobiological narrative. Collectively, these advancements not only augment our understanding of PD but also herald a new epoch of precise diagnostic and therapeutic stratagems.

MRI techniques have gained an esteemed position in the landscape of PD research and clinical applications. A salient feature of MRI's utility in PD management lies in its unparalleled diagnostic prowess. According to a seminal study by [44], MRI can meticulously discern between idiopathic PD and Atypical Parkinsonian Syndromes. This diagnostic differentiation, facilitated by MRI's ability to identify distinct neuroanatomical markers, is instrumental in tailoring patient-centric therapeutic regimens, thereby enhancing the precision of medical interventions. Moreover, as underscored by [29], MRI's longitudinal application serves as a conduit to trace the temporal trajectory of PD. By obtaining sequential MRI scans, clinicians are afforded a comprehensive vista into the evolving neurotopography of PD, enabling them to capture a spectrum of both structural and functional cerebral modifications attributable to the disorder's progression. Venturing into the therapeutic domain, MRI has emerged as an irreplaceable guide for surgical endeavors, specifically Deep Brain Stimulation (DBS). As elucidated by [45], the preoperative planning facilitated by MRI ensures exacting electrode placement during DBS procedures. This precision, in turn, not only optimizes therapeutic dividends but also significantly mitigates the risk of potential intraoperative complications.

3. Deep Learning-based MRI imaging analysis

The goal of DL-based imaging processing technology is to enhance clinical diagnosis by minimizing diagnostic complexity and errors, providing transparent information, and offering clear explanations to support medical professionals in their assessments. There are two primary applications in brain soft tissue imaging: soft tissue segmentation and diagnostic classification for distinguish- ing between right-handed and left-handed patients in PD diagnosis. Example studies with the contribution are summarized in Table 1.

DL constitutes a specialized domain within the broader field of AI and sets itself apart from traditional machine learning models. Convolutional neural networks (CNN) are frequently employed for classification tasks in image classification and segmentation challenges in computer vision [52–61]. CNNs demonstrate exceptional efficiency

Table 1. Summary of Contributions of Deep Learning in MRI Image Analysis.

Ref	Contribution	Results
[46]	Multi-atlas segmentation with motivation and strategies for atlas selection.	Assessed accuracy against fusion of random atlas sets.
[47]	Nonlocal patch-based segmentation for anatomical brain structures like the hippocampus and lateral ventricles.	Outperformed both appearance-based and template-based methods.
[48]	Multicontrast, multiecho MRI method for delineating the STN and other basal ganglia structures.	Enhanced STN delineation; provides valuable images for DBS planning and implantation.
[49]	Dual-contrast patch-based label fusion method for ROI segmentation using multivariate cross-correlation.	State-of-the-art performance in segmenting subthalamic nucleus, substantia nigra (SN), and red nucleus via MRI.
[50]	Studied contrast behavior of SN in magnetization transfer and susceptibility weighted imaging.	Elucidated SN volumes to aid in early-stage PD biomarker development.
[51]	UNet application for SN segmentation by linking anatomical and signal intensity information.	Validated via t-test distinguishes between healthy control and RBD patient groups.

when confronted with intricate patterns in image data, effectively handling nonlinear relationships, and are widely used in medical imaging diagnostics, such as for the classification of PD and healthy control. Their remarkable performance in medical imaging, coupled with the capability for parallelization using GPUs [62], has established CNNs as a cornerstone in the repertoire of tools utilized by the medical imaging research community. UNet is successfully implemented in medical image analysis, which was originally proposed for medical imaging segmentation to process the partition of an image into different regions. In contrast to the classical autoencoder architecture, which may encounter a bottleneck when utilizing encoder and decoder structures, UNet employs deconvolution on the decoder side to overcome this issue. This approach prevents the loss of features through connections from the encoder side. Various advanced network blocks with deep learning backbone models have been widely explored resulting in many promising approaches in medical imaging tasks [63–68]. It's worth noting that for 3D images, researchers have turned to utilizing 3D convolutions for conventional UNet known as 3D- UNet, as demonstrated in [69]. Another variation involves incorporating an attention module either before the encoder and decoder components or at the bottleneck of the UNet architecture, introduced by Attention UNet [70]. This addition is based on the concept that attention can be viewed as a technique for intelligently organizing computational resources to interpret the signal in an informative manner [71]. Similarly, PSPNet aims to improve image segmentation by addressing challenges like handling multi-scale information and context understanding [55]. It introduces a pyramid pooling module to capture information at various scales, enhancing segmentation performance. Its versatility and strong performance on benchmark datasets make it a valuable contribution to image semantic segmentation. However, it comes with limitations like computational complexity and data requirements. To further improve feature extraction on multi-scale levels, UNet++ builds upon the UNet architecture by enhancing feature extraction and context understanding through nested skip connections, which allow for better feature extraction at multiple scales [63]. This results in more accurate and fine-grained segmentation. To fully explore the sufficient information from full scales, UNet 3+ had been proposed by [72, 73] and this new approach uses full-scale skip connections and deep supervision to effectively handle organs of varying scales by combining low-level details and high-level semantics from different-scale feature maps. MultiResUNet is another extension of the UNet architecture that incorporates residual learning [74]. It processes information at multiple resolutions which allows to capture of fine details while maintaining global context, making it particularly effective for tasks that require precise segmentation and context understanding with residual learning [75].

Different from conventional UNet which is purely based on convolutional operations, transformers, a new model architecture named self-attention, has also been explored in image processing because of their success in natural language processing [76]. Researchers recognized that Transformers' self-attention with global context

capabilities could benefit computer vision tasks like object detection, image segmentation, and classification [76–79]. Additionally, the desire for a unified architecture capable of handling both text and images has driven the exploration of Transformers in vision tasks. Such as Vision Transformer (ViT) [77] has shown promise and has been adapted for medical imaging tasks. Different from ViT, Swin Transformer [79] uses a hierarchical processing strategy and employs linear self-attention which excels at multi-scale analysis and is more efficient. TransUNet has been proposed by [65], it offers advantages such as improved accuracy, reduced annotator dependence, versatility across medical imaging modalities, adaptability, and integration into clinical workflows. These benefits make it a promising tool for enhancing medical image segmentation and contributing to more accurate and efficient healthcare practices. Besides various different architecture of UNet with ViT-based layer, the promising performance, however, typically outperforms CNNs with a substantial amount of labeled data. It processes the images in a sequential manner, which may not be the most efficient way to capture spatial information. Various advanced DL training approaches hereby have been explored such as unsupervised domain adaptation, semi-supervised learning, and weakly-supervised learning [80–87].

Federated learning, aimed at enabling efficient, decentralized model train- ing, is a key study topic in MRI brain image analysis. This approach addresses data distribution imbalances and data privacy issues effectively. [88] highlights its relevance in smart healthcare, particularly in scenarios where large, diverse datasets are scarce. Federated learning (FL) facilitates collaborative ML model training without sharing sensitive patient data, a crucial advancement in scientific collaboration across medical research centers. [89, 90] further emphasize the advantages of FL in handling private medical image data, like 3D brain MRI scans, without breaching confidentiality. Their work introduces novel FL frameworks that address cross-site data heterogeneity, demonstrating improved accuracy in diagnostic tasks. [91] showcase FL's ability to maintain data privacy in brain tumor identification from MRI images with minimal performance com- promise [92] provide a comprehensive overview of FL's role in early brain tumor diagnosis, underscoring its accuracy and potential in AI-assisted diagnosis. [93] identify FL as a solution to the challenges of building robust AI models with

small, unlabeled datasets in medical imaging, enhancing global model performance while preserving patient privacy. These studies collectively affirm the significant role of federated learning in advancing MRI brain image analysis while safeguarding data privacy.

Domain adaptation is a training strategy that allow model transfer knowledge to tackle with other medical imaging tasks. Kermany DS et al. used an Inception V3 architecture pre-trained on the ImageNet dataset [85] which contains 108312 optical coherence tomography (OCT) images and they got an accuracy of 96.6%, with a sensitivity of 97.8%, a specificity of 97.4%, and a weighted error of 6.6%. Besides that, the Area Under Curve (AUC) of the Receiver operating characteristic (ROC) value is 99.9%, demonstrating the model's extraordinary ability to differentiate between various disease categories. Magesh PR, Myloth RD, and Tom RJ [86] have applied transfer learning to train the VGG16 CNNs on DaTscans from the Parkinson's Progression Markers Initiative (PPMI) database to classify PD and healthy control. Impressively, the model achieved outstanding performance: 95.2% accuracy, 97.5% sensitivity, and 90.9% specificity. To enhance interpretability, they used the Local Interpretable Model-Agnostic Explanations (LIME) explainer, which involved visual superpixels for deeper insights into the model's classifications. Model training with limited annotations such as semi- and weakly-supervised learning is also an essential area. Consistency regularization, also known as consistency-aware training, is a key concept and it aims to ensure the model maintains similar predictions under various data and model perturbations [94]. The data that is not annotated can be potentially extended with a pseudo label according to the prior knowledge [25, 95]. Another common strategy of training with limited data is adversarial training [96]. An additional model is developed to classify the quality of pseudo label in an iterative manner against the model while training [97, 98].

4. Deep Learning-based MRI imaging analysis in longitudinal settings

The above model architectures have consistently demonstrated their ability to enhance model performance across various adaptations. Nevertheless, it's important to note that there have been relatively few studies conducted in a longitudinal setting for PD disease. Siamese architecture is a type of neural model design that uses twin subnetworks with shared weights [99]. It is primarily used for similarity or dissimilarity learning tasks, such as face recognition or signature verification. Siamese models take two input samples and process them through identical subnetworks to measure the similarity or dissimilarity between them, it can better reduce the distance of sample values between unchanged regions and increase the distance of samples in changed regions. This architecture is particularly effective at learning how to differentiate between pairs of data points and is commonly employed in tasks that involve comparing and classifying objects or patterns.

Based on that, in 2018, Bhagwat N et al. [100] employed a Longitudinal Siamese Network (LSN) to predict the onset of Alzheimer's disease. They utilized MRI data of the same individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarker and Lifestyle Flag- ship Study of Ageing (AIBL), comparing two early time points to the baseline scan. Their model exhibited remarkable accuracy, achieving high accuracy and an impressive AUC for binary tasks. In 2022, Tao Chen et al. [101] also proposed a new Siamese neural model based on UNet (Siamese_UNet) with two parts for change detection in high-resolution remote sensing images. The Siamese_UNet comprises two main parts: a feature extraction Siamese model and a decoding section used to analyze feature differences between baseline and follow-up images of the same individuals. Their model achieved the highest F1 and Dice metrics while maintaining similar levels of precision and recall accuracy compared to other models, including DASNet, UNet, AUNet, and Siamese Net. Another approach, as demonstrated by Xu F et al. [102], involves the use of LSTM-UNet. In their model, they combined a multi-modal UNet with convolutional Long Short-Term Memory (LSTM). The UNet component incorporates a hyper-dense encoder and decoder to effectively harness multi-modal data and the convolutional LSTM leverages sequential information between consecutive brain segmentations. Their model boosted the model performance compared to the standard UNet with fewer model parameters.

Other model structures have also been proposed, [103] proposed a feature encoding algorithm based on a stacked sparse auto-encoder (SSAE) for training on longitudinal multi-modal PD data from the Parkinson's Progression Markers Initiative (PPMI) study, even when dealing with a small sample size. Their model exhibited superior performance compared to other structures, such as stacked auto-encoders (SAE), deep belief networks (DBN), and CNN, demonstrating its efficient handling of small datasets without overfitting. Notably, the regularization term and sparse constraints integrated into SSAE enable it to capture complementary features from different modalities effectively and amplify temporal differences in longitudinal data. [104] introduced a sophisticated three-stage deep learning ensemble approach. In the initial stage, they employed three distinct methods to extract spatiotemporal features from baseline DaTscan images. These methods included convolutional LSTM, CNN models such as VGG16 [105], ResNet50 [75], DenseNet121 [106], and InceptionV3 [107], and finally, an LSTM network for extracting features from maximum intensity projections (MIPs) of DaTscan transaxial image slices. Moving to the second stage, they utilized LSTM to extract temporal features from the baseline MDSUPDRS-III time sequences. In the ultimate stage, they amalgamated the features extracted from Stages 1 and 2 with other non-imaging clinical measures, such as age, gender, and duration of illness. These features were then fed into a fully connected layer to produce predictive outcomes.

However, the longitudinal PD imaging data currently available in research studies typically consist of only a few repeated measurements. This limited data may not effectively capture the disease progression trends and individual variabilities, especially considering that PD is a chronic neurodegenerative disease that often spans many years. Therefore, it is advisable to consider supplementing the dataset with additional data collected from a clinical

perspective. Another note is that this will require significantly greater computational power as the number of measurements increases.

5. Discussion

In this short survey, we have explored the latest advancements in state-of-the- art deep learning techniques proposed for PD diagnosis. However, it is noteworthy that there is a significant gap in available PD diagnostic approaches that specifically consider handedness within the framework of deep learning models. The aforementioned deep learning model have the potential to be effectively employed in the investigation of discrepancies between neuroimaging data from left-handed and right-handed PD patients, particularly in a longitudinal context. Longitudinal analysis is crucial because it allows researchers to capture the dynamical progression or changes in disease characteristics over time, and discover time-varying biomarkers used for early diagnosis or monitoring, as well as the time-varying features extracted from brain imaging. It facilitates the monitoring of disease evolution within individuals or populations, aiding the customization of personalized treatment strategies and interventions while providing insights into the disease's natural history and its various stages. Moreover, it continuously evaluates the effectiveness of treatments or interventions, drawing from changes in disease symptoms observed in imaging data. Furthermore, longitudinal analysis extends the capabilities of CNN models, which often focus solely on imaging segmentation or disease classification, by harnessing CNN's predictive power and feature extraction alongside clinical risk factors. This approach enables the identification of risk factors, predictive markers, and the revelation of cyclic or episodic patterns contributing to disease development or progression. While the rapid advancements in deep learning for PD diagnosis hold great promise, it's essential to recognize that disease heterogeneity, data quality, and labeling accuracy are critical factors influencing model performance. For in- stance, the diversity in imaging modalities, limited sample sizes, variations in imaging quality, and the presence of noisy labels can introduce prediction biases. Additionally, it's worth noting that large deep learning models can easily overfit the training dataset, leading to generalization issues. Another potential concern to be addressed is the presence of spurious correlations. In addition to the limitations mentioned earlier, the interpretability of the model also hinders its acceptance in clinical diagnosis. The process by which the model acquires the ability to identify relevant features and their connections does not mimic the learning process of radiologists in pathology diagnosis. The AI's primary goal is to uncover intricate features and interactions that might have initially evaded human observation. Nonetheless, it remains crucial that the newly unearthed insights are validated and confirmed by radiologists. In clinical diagnosis, the newly discovered knowledge must be verifiable by the radiologist [15].

6. Conclusion

In summary, our study underscores the prevailing trends in deep learning methods utilized for PD diagnosis. We emphasize the critical clinical need to advance the modeling paradigm within a longitudinal context. Typically, PD diagnostic imaging is gathered from patients who have already received confirmed diagnoses, often at an advanced stage with noticeable motor symptoms [108]. Consequently, there is an urgent demand for the development of disease progression models to aid in the early identification of biomarkers. Furthermore, it is essential to integrate the expertise of radiologists into the imaging processing workflow. This integration offers a "supervised" manner and facilitates transparent knowledge sharing between clinical professionals and model engineers. This collaborative effort will not only enhance the predictive capabilities of the final model but also establish an interactive framework that supports informed decision-making both forward and backward in the diagnostic process.

Decentralized federated learning, another key area for future development, provides a practical solution to address data distribution imbalances, data privacy issues, and resource limitations in scenarios with unevenly distributed and smaller sites in the medical imaging field. It will enable efficient model training while safeguarding data security and communication efficiency, emphasizing the significance of collaborative community efforts in its advancement and adoption. Despite the current challenges, we envision promising opportunities in the future. With the increasing availability of data and enhanced imaging processing capabilities, deep learning will empower clinical professionals to conduct more profound explorations into disease diagnosis and progression. This, in turn, holds the potential for discoveries in drug development and treatment options.

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Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

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