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Chapter 9
Automatic Diagnosis of Parkinson's Disease Based on Deep Learning Models and Multimodal Data

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ABSTRACT

Parkinson's disease (PD) is a common age-related neurodegenerative disorder in the aging society. Early diagnosis of PD is particularly important for efficient intervention. Currently, the diagnosis of PD is mainly made by neurologists who assess the abnormalities of the patient's motor system and evaluate the severity according to established criteria, which is highly dependent on the neurologists' expertise and often unsatisfactory. Artificial intelligence provides new potential for automatic and reliable diagnosis of PD based on multimodal data analysis. Some

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deep learning models have been developed for automatic detection of PD based on diverse biomarkers such as brain imaging images, electroencephalograms, walking postures, speech, handwriting, etc., with promising accuracy. This chapter summarizes the state-of-the-art, technical advancements, unmet research gaps, and future directions of deep learning models for PD detection. It provides a reference for biomedical engineers, data scientists, and health professionals.

INTRODUCTION

Unmet Clinical Need for the Diagnosis of Parkinson's Disease (PD)

Parkinson's disease (PD) is the second most common chronic progressive neurodegenerative condition worldwide. PD mainly occurs in individuals aged 50 years and above with motor symptoms include resting tremor, muscle tonus, and bradykinesia, and non-motor symptoms such as sleep dysfunction, dysgeusia, and cognitive deficits, etc. (Alzubaidi et al., 2021; D'Sa et al., 2023; Giannakopoulou et al., 2022). Males are more susceptible to the PD than females. The disease progresses gradually over time, negatively affecting the patient's daily life (Barua et al., 2021). The pathology of PD is not fully clear. Current clinical interventions include medication and surgery to alleviate symptoms, but a complete cure for PD has not yet been found (E et al., 2021; Guo et al., 2022; Suri et al., 2022). The high cost of treatment is a significant economic burden on patients, their families, and the society (H. W. Loh et al., 2021).

Age is the most significant and unalterable risk factor for PD, while genetic, environmental, and behavioral factors also play a role (Barua et al., 2021; Tolosa et al., 2021). As the global population ages, the prevalence of PD increased dramatically with disability-adjusted life years worldwide (Giannakopoulou et al., 2022), and early identification and diagnosis of patients in the disease's early stages is crucial to improve treatment efficiency and prognosis (Oliveira et al., 2023). Aging is associated with the decrease in dopamine secretion in neurons in the human brain. The pathological hallmark of PD consists of involute neuronal inclusions in the form of Lewy bodies and Lewy neurites with loss of neurons along the substantia nigra and other regions of the brain (Tolosa et al., 2021). However, the exact etiology of PD is still unclear. Although various pathophysiologic findings have aided in diagnosing PD, they do not enable clinicians to distinguish PD patients from healthy subjects.

At present, PD is diagnosed by reviewing the patient's medical history, symptoms, signs, and examination outcomes. The symptoms are evaluated through scales, e.g., the Movement Disorders Society Sponsored Revision of the Unified Parkinson's

Disease Rating Scale (MDS-UPDRS) and the Hoehn and Yahr (H&Y) Staging Scale (Giannakopoulou et al., 2022). Radiological examinations, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) can highlight the pathological changes in brain regions, providing reference for the detection of PD. However, there is no standardized imaging protocol for the detection of PD. In addition, it is difficult to exclude the confounding effects of other age-associated neurological diseases. With the lack of understanding of the underlying pathophysiology and the subjective nature of the diagnostic process, early and accurate of PD is still an unmet challenge (Alzubaidi et al., 2021; H. W. Loh et al., 2021; Xu et al., 2023).

Deep Learning Models and Potential for Detecting PD: An Overview of the State of the Art

Computer-aided diagnostic (CAD) systems can assist neurologists to comprehensively analyze the pathological features, providing new potentials for the early detection of PD (Bhachawat et al., 2023). CAD tools enhanced by artificial intelligence, i.e., machine learning or deep learning (DL) algorithms, can enable automated detection of PD based analysis of relevant biomarkers extracted from multimodal data, e.g., electroencephalogram (EEG) signals, gait posture, articulation, and radiological imaging data (H. W. Loh et al., 2021; Segato et al., 2020). DL has flourished in recent years and has excelled in various applications including image processing, natural language processing, and sequential signal processing. DL algorithms are capable of handling large-scale raw data and automatically extracting deep features, eliminating the need for feature selection and extraction which is a common limitation of machine learning models (Lee et al., 2017; H. W. Loh et al., 2021). DL algorithms have unique advantages in the quantitative analysis of multimodal, multidimensional big data, which is impossible in traditional clinical diagnosis made by neurologists. DL techniques have been used in examining brain imaging data and routine clinical examination results of many neurological disease, where the translational application in PD may generate new potentials in the early diagnosis (Giannakopoulou et al., 2022). DL models for the diagnosis of PD have been proposed using various types of data, including brain images and biosignals (PET, MRI, and EEG), as well as motor symptoms (gait, handwriting, speech) (H. W. Loh et al., 2021). The DL models may extract PD-associated features that are often neglected or difficult to detect in clinical practice (Giannakopoulou et al., 2022).

Artificial neural network (ANN) is a machine learning model consisting of three primary layers, i.e., input layer, hidden layer and output layer (Krogh, 2008). When an ANN model is integrated into an architecture with multiple hidden layers, the system is referred to as a deep neural network (DNN). DNN can process complex data

with high precision (Lee et al., 2017). Other classes of models such as Convolutional Neural Networks (CNN), Recurrent Neural Network (RNN), and the Long Short-Term Memory (LSTM) are constructed based on the primary architecture of DNN (H. W. Loh et al., 2021). CNN has been commonly used for image recognition and classification. RNN and LSTM are recognized for their capacity to detect patterns in sequential data, providing new potentials in the initial diagnosis of PD based on monitoring data (Chintalapudi et al., 2022).

LITERATURE REVIEW AND BACKGROUND

Literature Search Strategy

We reviewed recent studies in mainstream databases (PubMed and Web of Science) using the following keywords: deep learning AND Parkinson's disease AND (diagnosis OR detection). 357 papers are found and 177 papers are included for analysis after the screening based on the titles and abstracts. There are relatively few comprehensive comparisons of different DL models for early detection of AD. Figure 1 shows the word cloud of the included studies.

Figure 1. Word cloud of the included studies

Convolutional Neural Network (CNN)

CNNs are a type of artificial neural networks commonly applied in image analysis. A CNN model consists of multiple layers, each performing a specific task. The CNN input layers include convolutional and pooling layers, where the convolutional layer contains multiple filters for extracting features from the input images, producing multiple feature maps which are developed by training (Figure 2) (H. W. Loh et al., 2021; Hui Wen Loh et al., 2021). Subsequent convolution and pooling layers optimize the features and decrease the spatial dimensionality of feature mapping, which minimizes the possibility of overfitting and makes the network less computationally complex and more adaptable to the changes of input. The output of the feature mapping of the final pooling layer is flattened to a single list vector (Figure 2) (Lee et al., 2017; H. W. Loh et al., 2021). The fully connected layer is responsible for the features extracted from the single list vector and performs the final image classification. CNNs are commonly used for image recognition and classification, such as target detection, scene segmentation, and lesion detection on medical images (Lee et al., 2017; H. W. Loh et al., 2021).

Figure 2. Basic architecture of a convolutional neural network (CNN) model

Recurrent Neural Network (RNN)

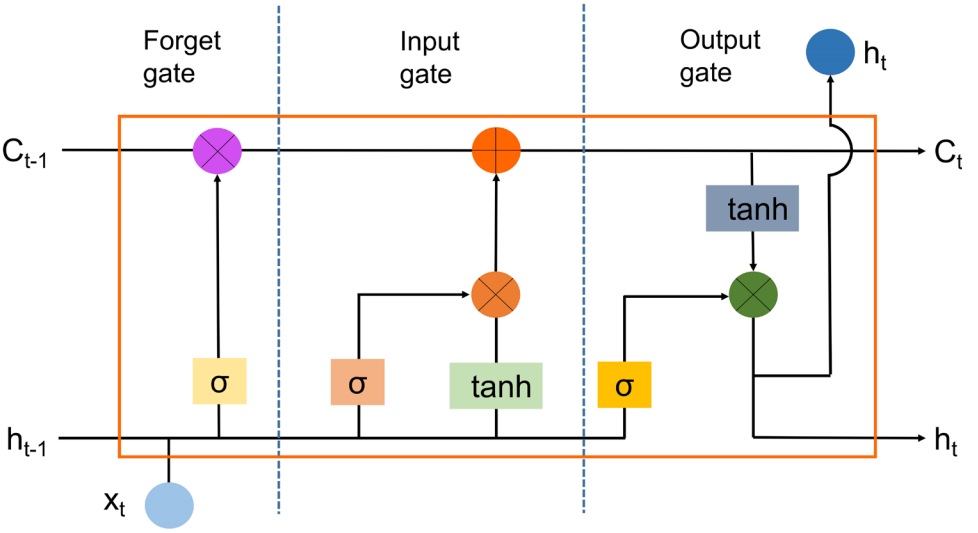
RNN creates a sequential representation of longitudinal data, where the inherent storage units can store previous network outputs and use them as inputs for future computations, which enhances the network's ability of decision making based on time series data (Balderas Silva et al., 2018; Chintalapudi et al., 2022). However, due to the lack of a control system, exploding and vanishing gradients are common concerns in RNN models. As a result, basic RNN models are often unable to learn data with long term dependencies (H. W. Loh et al., 2021; Loh et al., 2020).

Long Short-Term Memory (LSTM)

LSTM can overcome the shortcoming of RNN in vanishing gradients by introducing blocks of memories instead of self-connected implicit units (E et al., 2021; H. W.

Loh et al., 2021; Loh et al., 2020). A typical LSTM model includes a memory block and a memory unit in the hidden layer (Jiang et al., 2019). The memory block adopts a unique gate structure that contains three gate units, i.e., an input gate, a forgetting gate, and an output gate, which operate in unison to embody the LSTM function and manage the information flow (Jiang et al., 2019; H. W. Loh et al., 2021). To prevent the negative impact from irrelevant inputs, multiplicative gate units are employed. The input gate determines what information (xt) can be stored in the memory cell based on present input vector. The forgetting gate controls which information should be kept or forgotten in the memory cell. The output gate layer determines which output to be forwarded at each time step and which information to output as a hidden state (ht) (Jiang et al., 2019). The solution to the vanishing gradient problem resides in the forgetting gate, which employs a function to decide whether to retain or discard the information of previous cell state (Ct-1). By eliminating irrelevant data and appropriately resetting the information inherited from the current inputs, the large discrepancy that occurs between the old and new information can be addressed (Jiang et al., 2019; H. W. Loh et al., 2021). LSTM substitutes each conventional node in the implicit layer with a memory unit with the ability that learns long-term dependencies between successive sets of data, enabling the storage of, and access to, the information across extended periods (E et al., 2021). The capabilities of LSTM models in pattern recognition and time series prediction enable wide application scenarios such as speech and handwriting recognition, machine translation, air pollution prediction, and weather forecasting (E et al., 2021).

Figure 3. Basic structure of a long short-term memory (LSTM) unit. h_{t-1}: the previous block output; x_t: the input vector ; σ: the sigmoid function; tanh: a tanh function; C_{t-1}: the previous cell state; C_t: the cell state at time t; h_t: the hidden output. Inspired by Balaji et al. (2021).



RECENT DEEP LEARNING MODELS IN CLINICAL APPLICATIONS

Brain Imaging Analysis

Some state-of-the-art DL models with novel architectures have been proposed and effectively applied in medical image analysis. MRI, PET, and single-photon emission computed tomography (SPECT) are fundamental brain imaging procedures commonly utilized in the diagnosis of PD at early stages. For MRI, Chakraborty et al. utilized 3D MRI images of the entire brain for to capture the complex patterns of all subcortical brain structures. After data preprocessing, a 3D CNN structure was developed and cross-validated to detect PD, with an accuracy of 95.3% (Chakraborty et al., 2020). Piccardo et al. used 3D CNN to analyze brain PET and identify PD patients with nigrostriatal neurodegeneration, achieving 93% accuracy (Piccardo et al., 2021). Sun et al. developed a novel DL-based radiomics model fed by [18F] fluorodeoxyglucose (FDG) PET images and validated it with an accuracy of 95.17% in diagnosing PD (Sun et al., 2022). As to SPECT, Kurmi et al. proposed an integrated CNN (Fuzzy Rank Level Fusion) model to detect PD using dopamine transporter (DaT) scan images, achieving the highest accuracy of 98.8% (Kurmi et

al., 2022). SPECT imaging has shown superior modeling performance to MRI and PET imaging for automated PD detection, partly because of its ability to detect DaT with the radiotracer Iodofluran-123 (Choi et al., 2017), which reflects the loss of dopamine neurons in the brain of PD patients (Garibotto et al., 2013; H. W. Loh et al., 2021). CNN models perform well in identifying PD from healthy controls based on brain image analysis and deserve further exploration.

EEG and ECG Signal Analysis

EEG signals detect electrophysiological activity in the brain by standardized electrodes placed on the scalp (Shah et al., 2020). PD can change the dynamic properties of the EEG due to the progressive death of dopamine-releasing neurons and alterations in the anatomical structure of the brain (Shah et al., 2020) . Oh et al. utilized a CNN model to differentiate the EEG signals of 20 patients with PD and 20 normal subjects with a binary classification accuracy of 88.25% (Oh et al., 2020). Chu et al. used structured power spectral density with spatial distribution as an input to CNN to detect personalized anomalies in spatial spectral features of EEG in early-stage PD patients with an accuracy of 99.87% (Chu et al., 2021). Some studies suggested the combination of CNN and RNN models, among which Shah et al. proposed a Convolutional Recurrent Neural Network (CRNN) model that extracted sufficient spatial and temporal features from multichannel EEG signals, which achieved 99.2% accuracy in detecting PD (Lee et al., 2021). Khare et al. introduced a CNN architecture using Smoothed Pseudo-Wignerville distribution attributes of EEG signals as input in the best performing model, achieving nearly 100% accuracy (Khare et al., 2021).

Cardiac autonomic dysfunction is present in the early stages of PD and can be reflect by electrocardiogram (ECG) signals. Yoo et al. developed a CNN model consisting of 16 layers to detect PD based on ECG data and cross-validated it with 86.9% accuracy (Yoo et al., 2023). ECG could serve as a potential indicator for diagnosing PD while further validation is needed.

Gait Recognition and Pose Estimation

PD is featured by a motor syndrome that includes bradykinesia, resting tremor, rigidity, and altered posture and gait; therefore, assessment of body movement can also aid in the diagnosis of PD (Tolosa et al., 2021). Currently, PD-related evaluations comprise assessments of gait, handwriting, speech, and other motor-related tests. Gait disorders may worsen with the progression of PD. Currently, gait analysis focuses on gauging the severity of gait disturbances and detecting the episodes of freezing (di Biase et al., 2020). El Maachi et al. processed 18 one-dimensional signals from

a foot sensor measuring vertical ground reaction force by constructing a classifier using a one-dimensional CNN, ultimately achieving 98.7% classification accuracy (El Maachi et al., 2020). CNN can automatically learn valuable features from given gait data, and LSTM is widely used for gait recognition because they are good at dealing with time series with long intervals and multiple classification problems (Xia et al., 2020). Xia et al. developed a DL-based bimodal model with left and right gaits modeled respectively by CNN and LSTM, both trained and tested on sequential data of one-dimensional vertical ground reaction force signals across different gait cycles, obtaining a high accuracy of 99.31% in detecting PD (Xia et al., 2020). The DL-enhanced gain recognition provides a possible approach for early detection of PD in daily monitoring.

With the advancement of computer vision technology, there has been significant development in human pose estimation algorithms. In vision-based gait analysis, locating the joints of an individual in an image or video has been used to achieve human pose estimation (Zhang et al., 2023). Zhang et al. accurately identified PD gait in forward walking video with 87.1% accuracy using a weighted adjacency matrix with virtual connectivity and a multiscale temporal convolutional network(Zhang et al., 2023). Chen and colleagues placed sensors at the wrists, ankles, and hips to collect motion data from participants during 10 m walking trials, and constructed CNN classification models. They found that the hip sensors had the highest classification performance, with an accuracy of 98.01% in detecting PD (Chen et al., 2023).

Vocal Signal Analysis

Patients with PD struggle with movement due to muscle stiffness which impairs their ability to speak normally, e.g., decreased volume, slurred speech (Nijhawan et al., 2023). Vocalization disorder is amongst the earliest symptoms of PD. A variety of DL models have been proposed to detect PD by analyzing speech signals which are nonlinear, nonsmooth signals with oscillatory properties, where the performance depends on the both feature extraction and classification algorithms (Hireš et al., 2022; Mian, 2022; Nijhawan et al., 2023). Goyal et al. proposed a hybrid approach combining resonance component analysis and time-frequency domain features, where a CNN classifier was fed by a hybrid dataset to detect PD achieving 99.4% accuracy (Goyal et al., 2021). Nagasubramanian et al. developed a CNN-based multivariate speech data analysis approach which achieved an accuracy rate of 99.5% in detecting PD (Nagasubramanian & Sankayya, 2021). Ali et al. developed a hybrid intelligent system for automatic acoustic analysis of speech signals using linear discriminant analysis to reduce dimensionality where the hyperparameters were optimized by a genetic algorithm, with nearly 100% classification accuracy (Ali et al., 2019). CNN

models have been widely used for speech signal analysis while clinical trials are needed for full validation.

Handwriting Dynamics Assessment

Dysgraphia is a primary symptom of PD. As the disease progresses, the patient's ability to write deteriorates. Micrographia (abnormally small letter sizes) is a common and easily detectable writing abnormality among PD patients (Rios-Urrego et al., 2019). To differentiate handwritten images of PD patients from healthy controls, the majority of proposed deep learning methods utilize CNN models, and datasets like HandPD, NewHandPD, and Parkinson's Drawing are commonly employed (Kamran et al., 2021; Pereira et al., 2016). Pereira et al. presented the "NewHandPD" dataset, which captures signals recorded from patients with PD and healthy people through a smart pen, and developed a CNN model to learn features of handwriting dynamics with an accuracy about 95% in detecting PD (Pereira et al., 2018). Kamran et al. combined PaHaW dataset, HandPD, NewHandPD, and Parkinson's Drawing datasets and used a deep migration learning-based algorithm to overcome the high variability of handwritten materials and achieved high accuracy of 99.22% in PD detection (Kamran et al., 2021). Speech and handwritten recordings are easier and less costly compared to brain imaging, and have a greater potential in population screening of PD patients.

Multimodal Data Analysis

Given the heterogeneous and complex nature of PD progression, along with the challenges in continuously tracking all relevant metrics, multimodal data analysis is essential for the detection of PD and severity evaluation in real-world settings (Skaramagkas et al., 2023). Multimodal data are generated from different technical approaches, including imaging modalities such as SPECT, PET, MRI, etc., and/or clinical tests such as cognitive and motor tests (Zhang, 2022). Deep learning has unique advantages in multimodal data analysis, enabling the integration of heterogeneous information for detecting PD. Vásquez-Correa et al. proposed a CNN model to identify PD patients based on their difficulties in commencing or terminating movements from speech, handwriting, and gait information, where the integration of three biosignals derived a promising accuracy of 97.3% (Vásquez-Correa et al., 2019). Pahuja and Prasad developed feature-level and modal-level CNN frameworks to classify diagnosed PD patients and healthy controls using a hybrid dataset of neuroimaging (T1-weighted MRI scans and SPECT) and biological (cerebrospinal fluid) features, with maximum accuracy of 93.33% and 92.38% in feature-level and modal-level frameworks (Pahuja & Prasad, 2022).

DISCUSSION

Summarization of the State of the Art

The existing DL model have shown great potential for early diagnosis of PD. The performance metrics are above 90% in many studies (Table 1). MRI, SPECT and DaTSCAN imaging datasets, obtained mainly from the Parkinson Progression Markers Initiative (PPMI) are widely used to train the classifiers (Chakraborty et al., 2020; Kurmi et al., 2022; Ozsahin et al., 2020). CNN is the most commonly used DL model, which has achieve high performance in image classification (Kurmi et al., 2022) and the analysis of one-dimensional signals such as EEG and speech (Goyal et al., 2021; Khare et al., 2021) . Gait analysis performs better when using hybrid model CNN-LSTM model (Xia et al., 2020). Outstanding results have been achieved based on CNN and Deep Migration Learning in a study focusing on classification of handwritten images to recognize PD at an early stage (Kamran et al., 2021). In addition, Ozsahin et al. and Ali et al. used back propagation neural network and Genetically Optimized Neural Network models which achieved the highest prediction accuracy in SPECT and speech analysis respectively (Ali et al., 2019; Ozsahin et al., 2020). Since the majority of existing studies are based on unimodal data using different datasets, it is difficult to conclude on the best DL model (H. W. Loh et al., 2021). These studies demonstrated the potential of specific DL models for PD diagnosis provided references for future exploration (Garcia Santa Cruz et al., 2023).

Table 1. Summary of deep learning models to detect Parkinson's disease

Study	Sample size	Input Feature	Methods	Performance(%)
(Chakraborty et al., 2020)	203 PD and 203 HC (PPMI)	MRI Scans Images	CNN	Accuracy=0.953 Specificity=0.943 AUC=0.98
(Kurmi et al., 2022)	432 PD and 213 HC (PPMI)	DaT scan Images	CNN	Accuracy=0.985 Specificity=0.977 Sensitivity=0.988
(Ozsahin et al., 2020)	1334 PD and 212 HC (PPMI)	DaT scan Images	Back Propagation Neural Network	Accuracy=0.996 Specificity=0.992 Sensitivity=0.997
(Piccardo et al., 2021)	43 PD and 55 HC (private)	[18F]DOPA PET/CT scan Images	CNN	Accuracy=0.93 Specificity=0.89 Sensitivity=1 ROC(AUC)=0.882
(Sun et al., 2022)	125 PD and 281 HC (combination of 2 database)	[18F]FDG PET scan Images	Deep Learning-based Radiomics	Accuracy=0.952 Specificity=0.889 Sensitivity=0.978 ROC(AUC)=0.90
(Lee et al., 2021)	20 PD and 22 HC	EEG	CNN and RNN	Accuracy=0.992 ROC(AUC)=0.99
(Khare et al., 2021)	15 PD and 16 HC (public)	EEG	Parkinson's disease CNN	Accuracy=1
(Xia et al., 2020)	93 PD and 73 HC (public)	Gait	CNN and LSTM	Accuracy=0.993 Specificity=0.992 Sensitivity=0.994
(Goyal et al., 2021)	16 PD, 21 HC and 20HC	Speech	CNN	Accuracy=0.994
(Ali et al., 2019)	20 PD and 20 HC	Speech	Genetically Optimized Neural Network	Accuracy=1 Sensitivity=1
(Pereira et al., 2018)	74 PD and 18 HC	Handwriting	CNN	Accuracy=0.935
(Yoo et al., 2023)	751 PD and 751 HC	ECG	CNN	Accuracy=0.869 ROC=0.924
(Vásquez-Correa et al., 2019)	44 PD and 40 HC	Multimodal data	CNN	Accuracy=0.976

N.B: PD, Parkinson's disease; HC, healthy control; PPMI, Parkinson Progression Markers Initiative; ROC, receiver operating characteristic curve; AUC, area under curve; CNN, Convolutional Neural Networks; RNN, Recurrent Neural Network; LSTM, Long Short-Term Memory. EEG, electroencephalogram; ECG, electrocardiogram.

Advantages of Deep Learning in the Diagnosis of PD

Currently, the diagnosis of PD is determined primarily by neurology based on a clinical feature set that is highly subjective and prone to perceived error, with suboptimal clinical diagnostic accuracy reported for movement disorder specialists (Parajuli et al., 2023). The DL models enable the extraction of relevant deep information from large multimodal datasets of PD, providing higher accuracy and sensitivity in early diagnosis of PD. The application of DL models may contribute to clinical decision-making towards personalized treatment and efficient management to reduce the burden on healthcare professionals. The results may reveal underlying pathophysiological mechanisms.

Limitations, Challenges, and Future Directions

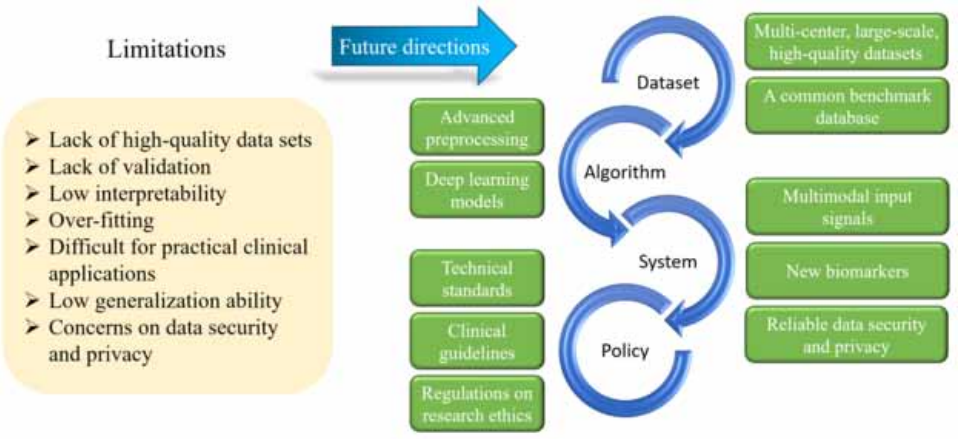
A good DL model for clinical practice should provide end-users with reliable reference on disease diagnosis with adaptability on different cohorts and application scenarios. Despite the high performance existing DL models, there are some limitations and challenges to be addressed before the DL models can be translated into real-world clinical practice (Figure 4).

Firstly, most of the current DL models are based on small, unimodal datasets rather than using large-scale multimodal datasets. This is attributed to the lack of high-quality datasets and the research gaps in reliable data fusion algorithms. As a result, overfitting is common problem for DL-assisted CAD tools where the performance could be overestimated (Pahuja & Prasad, 2022). On the other hand, existing DL models lack large-scale validation on real-world clinical data from different cohorts. The lack of large-scale validation also compromises the interpretability and generalization ability of the models. In clinical practice, it is essential for neuroscientists to understand the underlying mechanisms and relevant factors behind the results provided by DL models. Considering the diversity in disease progression between patients, the DL models based on unimodal data are unlikely to capture the underlying patterns of disease for reliable diagnose of PD. All these limitations make it difficult to develop reliable DL-assisted CADs and integrate them in current clinical practice (H. W. Loh et al., 2021; Paul et al., 2022; Varghese, 2020). Technically, towards fully-validated DL models, it its essential to process and analyze large multimodal datasets, which proposed challenges in data preprocessing, data fusion, and computational efficiency of the DL algorithms. Another limitations lies in the research ethics in these early-stage DL models based on open-source datasets, where patient privacy and security are often overlooked. The data security and patients' privacy are important concerns in real-world applications.

Data security and privacy are important concerns in real-world applications. On the one hand, personal information is at the risk of leakage during the sharing of PD-associated datasets. On the other hand, the DL algorithms themselves have privacy issues, including data leakage in the training phase, as well as model inversion attacks, black-box/white-box attacks, membership inference attacks, and model stealing attacks during application (Al-Rubaie & Chang, 2019; Rouani et al., 2019). Multi-party homomorphic encryption is a combination of homomorphic encryption and secure multi-party computation, which can protect privacy during data sharing. In addition, relaxed differential privacy can be considered in the training of DL models (Scheibner et al., 2021). Multiple technologies are combined to achieve privacy protection throughout the DL-based data analysis. Finally, the development of standards and regulations provides essential frameworks and guidance for the protection of privacy, participants' awareness, and data transparency.

In the future, improvements can be made in different dimensions (Figure 4). First, breaking the limitation of sample size, establishing benchmark databases, and introducing datasets with multimodal, multidimensional features can improve the generalization ability of DL algorithms and prevent overfitting. Second, the establishment of advanced data preprocessing and deep learning frameworks are essential for the processing of large-scale multimodal datasets. Third, towards a reliable, well-validated, and interpretable CAD system for clinical decision-making in real-world settings, it is imperative to consider the multimodal signals and data as the input, the ability to detect new biomarkers, and the data security solutions for privacy protection. Finally, there is high need for reshaping the healthcare ecosystem at policy level. The improvement of technical standards, the update of current clinical guidelines, and establishment of relevant regulations on research ethics and standardization will commonly improve the development of DL-enhanced CAD for early diagnosis of PD.

Figure 4. Limitations and future directions of deep learning methods for early detection of Parkinson's disease



CONCLUSION

The use of DL models has significant potential for early, personalized diagnosis of PD. Currently DL models have achieved high performance but limited by dataset, overfitting, lack of validation, low interpretability, low generalization ability, with concerns on data security. Future improvements in dataset, algorithm, system, and policy could overcome the current gaps and achieve DL-enhanced CAD applicable for early diagnosis of PD in real-world clinical settings.

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REFERENCES

Al-Rubaie, M., & Chang, J. M. (2019). Privacy-Preserving Machine Learning: Threats and Solutions. *IEEE Security and Privacy*, *17*(2), 49–58. doi:10.1109/MSEC.2018.2888775

Ali, L., Zhu, C., Zhang, Z., & Liu, Y. (2019). Automated Detection of Parkinson's Disease Based on Multiple Types of Sustained Phonations Using Linear Discriminant Analysis and Genetically Optimized Neural Network. *IEEE Journal of Translational Engineering in Health and Medicine*, *7*, 2000410. doi:10.1109/JTEHM.2019.2940900 PMID:32166050

Alzubaidi, M. S., Shah, U., Dhia Zubaydi, H., Dolaat, K., Abd-Alrazaq, A. A., Ahmed, A., & Househ, M. (2021). The Role of Neural Network for the Detection of Parkinson's Disease: A Scoping Review. *Healthcare (Basel)*, *9*(6), 740. doi:10.3390/healthcare9060740 PMID:34208654

Balderas Silva, D., Ponce Cruz, P., & Molina Gutierrez, A. (2018). Are the long–short term memory and convolution neural networks really based on biological systems? *ICT Express*, *4*(2), 100–106. doi:10.1016/j.icte.2018.04.001

Barua, P. D., Dogan, S., Tuncer, T., Baygin, M., & Acharya, U. R. (2021). Novel automated PD detection system using aspirin pattern with EEG signals. *Computers in Biology and Medicine*, *137*, 104841. doi:10.1016/j.compbiomed.2021.104841 PMID:34509880

Bhachawat, S., Shriram, E., Srinivasan, K., & Hu, Y.-C. (2023). Leveraging Computational Intelligence Techniques for Diagnosing Degenerative Nerve Diseases: A Comprehensive Review, Open Challenges, and Future Research Directions. *Diagnostics (Basel)*, *13*(2), 288. doi:10.3390/diagnostics13020288 PMID:36673100

Chakraborty, S., Aich, S., & Kim, H. C. (2020). Detection of Parkinson's Disease from 3T T1 Weighted MRI Scans Using 3D Convolutional Neural Network. *Diagnostics (Basel)*, *10*(6), 402. doi:10.3390/diagnostics10060402 PMID:32545609

Chen, M., Sun, Z., Xin, T., Chen, Y., & Su, F. (2023). An Interpretable Deep Learning Optimized Wearable Daily Detection System for Parkinson's Disease. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *31*, 1–1. doi:10.1109/TNSRE.2023.3314100 PMID:37695969

Chintalapudi, N., Battineni, G., Hossain, M. A., & Amenta, F. (2022). Cascaded Deep Learning Frameworks in Contribution to the Detection of Parkinson's Disease. *Bioengineering (Basel, Switzerland)*, *9*(3), 116. doi:10.3390/bioengineering9030116 PMID:35324805

Choi, H., Ha, S., Im, H. J., Paek, S. H., & Lee, D. S. (2017). Refining diagnosis of Parkinson's disease with deep learning-based interpretation of dopamine transporter imaging. *NeuroImage. Clinical*, *16*, 586–594. doi:10.1016/j.nicl.2017.09.010 PMID:28971009

Chu, C., Zhang, Z., Wang, J., Liu, S., Wang, F., Sun, Y., Han, X., Li, Z., Zhu, X., & Liu, C. (2021). Deep learning reveals personalized spatial spectral abnormalities of high delta and low alpha bands in EEG of patients with early Parkinson's disease. *Journal of Neural Engineering*, *18*(6), 066036. doi:10.1088/1741-2552/ac40a0 PMID:34875634

D'Sa, K., Evans, J. R., Virdi, G. S., Vecchi, G., Adam, A., Bertolli, O., Fleming, J., Chang, H., Leighton, C., Horrocks, M. H., Athauda, D., Choi, M. L., & Gandhi, S. (2023). Prediction of mechanistic subtypes of Parkinson's using patient-derived stem cell models. *Nature Machine Intelligence*, *5*(8), 933–946. doi:10.1038/s42256-023-00702-9 PMID:37615030

di Biase, L., Di Santo, A., Caminiti, M. L., De Liso, A., Shah, S. A., Ricci, L., & Di Lazzaro, V. (2020). Gait Analysis in Parkinson's Disease: An Overview of the Most Accurate Markers for Diagnosis and Symptoms Monitoring. *Sensors (Basel)*, *20*(12), 3529. doi:10.3390/s20123529 PMID:32580330

E, B., D, B., Elumalai, V. K., & R, V. (2021). Automatic and non-invasive Parkinson's disease diagnosis and severity rating using LSTM network. *Applied Soft Computing, 108*, 107463.

El Maachi, I., Bilodeau, G.-A., & Bouachir, W. (2020). Deep 1D-Convnet for accurate Parkinson disease detection and severity prediction from gait. *Expert Systems with Applications*, *143*, 113075. doi:10.1016/j.eswa.2019.113075

Garcia Santa Cruz, B., Husch, A., & Hertel, F. (2023). Machine learning models for diagnosis and prognosis of Parkinson's disease using brain imaging: General overview, main challenges, and future directions. *Frontiers in Aging Neuroscience*, *15*, 1216163. doi:10.3389/fnagi.2023.1216163 PMID:37539346

Garibotto, V., Montandon, M. L., Viaud, C. T., Allaoua, M., Assal, F., Burkhard, P. R., Ratib, O., & Zaidi, H. (2013). Regions of interest-based discriminant analysis of DaTSCAN SPECT and FDG-PET for the classification of dementia. *Clinical Nuclear Medicine*, *38*(3), e112–e117. doi:10.1097/RLU.0b013e318279b991 PMID:23357822

Giannakopoulou, K. M., Roussaki, I., & Demestichas, K. (2022). Internet of Things Technologies and Machine Learning Methods for Parkinson's Disease Diagnosis, Monitoring and Management: A Systematic Review. *Sensors (Basel)*, *22*(5), 1799. doi:10.3390/s22051799 PMID:35270944

Goyal, J., Khandnor, P., & Aseri, T. C. (2021). A hybrid approach for Parkinson's disease diagnosis with resonance and time-frequency based features from speech signals. *Expert Systems with Applications*, *182*, 115283. doi:10.1016/j.eswa.2021.115283

Guo, X., Tinaz, S., & Dvornek, N. C. (2022). Characterization of Early Stage Parkinson's Disease From Resting-State fMRI Data Using a Long Short-Term Memory Network [Original Research]. *Frontiers in Neuroimaging*, *1*, 1. doi:10.3389/fnimg.2022.952084 PMID:37555151

Hireš, M., Gazda, M., Drotár, P., Pah, N. D., Motin, M. A., & Kumar, D. K. (2022). Convolutional neural network ensemble for Parkinson's disease detection from voice recordings. *Computers in Biology and Medicine*, *141*, 105021. doi:10.1016/j.compbiomed.2021.105021 PMID:34799077

Jiang, C., Chen, Y., Chen, S., Bo, Y., Li, W., Tian, W., & Guo, J. (2019). A Mixed Deep Recurrent Neural Network for MEMS Gyroscope Noise Suppressing. *Electronics (Basel)*, *8*(2), 181. doi:10.3390/electronics8020181

Kamran, I., Naz, S., Razzak, I., & Imran, M. (2021). Handwriting dynamics assessment using deep neural network for early identification of Parkinson's disease. *Future Generation Computer Systems*, *117*, 234–244. doi:10.1016/j.future.2020.11.020

Khare, S. K., Bajaj, V., & Acharya, U. R. (2021). PDCNNet: An Automatic Framework for the Detection of Parkinson's Disease Using EEG Signals. *IEEE Sensors Journal*, *21*(15), 17017–17024. doi:10.1109/JSEN.2021.3080135

Krogh, A. (2008). What are artificial neural networks? *Nature Biotechnology*, *26*(2), 195–197. doi:10.1038/nbt1386 PMID:18259176

Kurmi, A., Biswas, S., Sen, S., Sinitca, A., Kaplun, D., & Sarkar, R. (2022). An Ensemble of CNN Models for Parkinson's Disease Detection Using DaTscan Images. *Diagnostics (Basel)*, *12*(5), 1173. doi:10.3390/diagnostics12051173 PMID:35626328

Lee, J. G., Jun, S., Cho, Y. W., Lee, H., Kim, G. B., Seo, J. B., & Kim, N. (2017). Deep Learning in Medical Imaging: General Overview. *Korean Journal of Radiology*, *18*(4), 570–584. doi:10.3348/kjr.2017.18.4.570 PMID:28670152

Lee, S., Hussein, R., Ward, R., Jane Wang, Z., & McKeown, M. J. (2021). A convolutional-recurrent neural network approach to resting-state EEG classification in Parkinson's disease. *Journal of Neuroscience Methods*, *361*, 109282. doi:10.1016/j.jneumeth.2021.109282 PMID:34237382

Loh, H. W., Hong, W., Ooi, C. P., Chakraborty, S., Barua, P. D., Deo, R. C., Soar, J., Palmer, E. E., & Acharya, U. R. (2021). Application of Deep Learning Models for Automated Identification of Parkinson's Disease: A Review (2011-2021). *Sensors (Basel)*, *21*(21), 7034. doi:10.3390/s21217034 PMID:34770340

Loh, H. W., Ooi, C. P., Palmer, E., Barua, P. D., Dogan, S., Tuncer, T., Baygin, M., & Acharya, U. R. (2021). GaborPDNet: Gabor Transformation and Deep Neural Network for Parkinson's Disease Detection Using EEG Signals. *Electronics (Basel)*, *10*(14), 1740. doi:10.3390/electronics10141740

Loh, H. W., Ooi, C. P., Vicnesh, J., Oh, S. L., Faust, O., Gertych, A., & Acharya, U. R. (2020). Automated Detection of Sleep Stages Using Deep Learning Techniques: A Systematic Review of the Last Decade (2010–2020). *Applied Sciences (Basel, Switzerland)*, *10*(24), 8963. doi:10.3390/app10248963

Mian, T. S. (2022). An Unsupervised Neural Network Feature Selection and 1D Convolution Neural Network Classification for Screening of Parkinsonism. *Diagnostics (Basel)*, *12*(8), 1796. doi:10.3390/diagnostics12081796 PMID:35892507

Nagasubramanian, G., & Sankayya, M. (2021). Multi-Variate vocal data analysis for Detection of Parkinson disease using Deep Learning. *Neural Computing & Applications*, *33*(10), 4849–4864. doi:10.1007/s00521-020-05233-7

Nijhawan, R., Kumar, M., Arya, S., Mendirtta, N., Kumar, S., Towfek, S. K., Khafaga, D. S., Alkahtani, H. K., & Abdelhamid, A. A. (2023). A Novel Artificial-Intelligence-Based Approach for Classification of Parkinson’s Disease Using Complex and Large Vocal Features. *Biomimetics*, *8*(4), 351. doi:10.3390/biomimetics8040351 PMID:37622956

Oh, S. L., Hagiwara, Y., Raghavendra, U., Yuvaraj, R., Arunkumar, N., Murugappan, M., & Acharya, U. R. (2020). A deep learning approach for Parkinson's disease diagnosis from EEG signals. *Neural Computing & Applications*, *32*(15), 10927–10933. doi:10.1007/s00521-018-3689-5

Oliveira, A. M., Coelho, L., Carvalho, E., Ferreira-Pinto, M. J., Vaz, R., & Aguiar, P. (2023). Machine learning for adaptive deep brain stimulation in Parkinson's disease: Closing the loop. *Journal of Neurology*, *270*(11), 5313–5326. doi:10.1007/s00415-023-11873-1 PMID:37530789

Ozsahin, I., Sekeroglu, B., Pwavodi, P. C., & Mok, G. S. P. (2020). High-accuracy Automated Diagnosis of Parkinson's Disease. *Current Medical Imaging*, *16*(6), 688–694. doi:10.2174/1573405615666190620113607 PMID:32723240

Pahuja, G., & Prasad, B. (2022). Deep learning architectures for Parkinson's disease detection by using multi-modal features. *Computers in Biology and Medicine*, *146*, 105610. doi:10.1016/j.compbiomed.2022.105610 PMID:35659446

Parajuli, M., Amara, A. W., & Shaban, M. (2023). Deep-learning detection of mild cognitive impairment from sleep electroencephalography for patients with Parkinson's disease. *PLoS One*, *18*(8), e0286506. doi:10.1371/journal.pone.0286506 PMID:37535549

Paul, S., Maindarkar, M., Saxena, S., Saba, L., Turk, M., Kalra, M., Krishnan, P. R., & Suri, J. S. (2022). Bias Investigation in Artificial Intelligence Systems for Early Detection of Parkinson’s Disease: A Narrative Review. *Diagnostics (Basel)*, *12*(1), 166. doi:10.3390/diagnostics12010166 PMID:35054333

Pereira, C. R., Pereira, D. R., Rosa, G. H., Albuquerque, V. H. C., Weber, S. A. T., Hook, C., & Papa, J. P. (2018). Handwritten dynamics assessment through convolutional neural networks: An application to Parkinson's disease identification. *Artificial Intelligence in Medicine*, *87*, 67–77. doi:10.1016/j.artmed.2018.04.001 PMID:29673947

Pereira, C. R., Weber, S. A. T., Hook, C., Rosa, G. H., & Papa, J. P. (2016, October 4-7). Deep Learning-Aided Parkinson's Disease Diagnosis from Handwritten Dynamics. *European Radiology*, *31*(9), 7003–7011.

Rios-Urrego, C. D., Vásquez-Correa, J. C., Vargas-Bonilla, J. F., Nöth, E., Lopera, F., & Orozco-Arroyave, J. R. (2019). Analysis and evaluation of handwriting in patients with Parkinson's disease using kinematic, geometrical, and non-linear features. *Computer Methods and Programs in Biomedicine*, *173*, 43–52. doi:10.1016/j.cmpb.2019.03.005 PMID:31046995

Rouani, B. D., Samragh, M., Javidi, T., & Koushanfar, F. (2019). Safe Machine Learning and Defeating Adversarial Attacks. *IEEE Security and Privacy*, *17*(2), 31–38. doi:10.1109/MSEC.2018.2888779

Scheibner, J., Raisaro, J. L., Troncoso-Pastoriza, J. R., Ienca, M., Fellay, J., Vayena, E., & Hubaux, J. P. (2021). Revolutionizing Medical Data Sharing Using Advanced Privacy-Enhancing Technologies: Technical, Legal, and Ethical Synthesis. *Journal of Medical Internet Research*, *23*(2), e25120. doi:10.2196/25120 PMID:33629963

Segato, A., Marzullo, A., Calimeri, F., & De Momi, E. (2020). Artificial intelligence for brain diseases: A systematic review. *APL Bioengineering*, *4*(4), 041503. doi:10.1063/5.0011697 PMID:33094213

Shah, S. A. A., Zhang, L., & Bais, A. (2020). Dynamical system based compact deep hybrid network for classification of Parkinson disease related EEG signals. *Neural Networks*, *130*, 75–84. doi:10.1016/j.neunet.2020.06.018 PMID:32650152

Skaramagkas, V., Pentari, A., Kefalopoulou, Z., & Tsiknakis, M. (2023). Multi-Modal Deep Learning Diagnosis of Parkinson's Disease—A Systematic Review. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *31*, 2399–2423. doi:10.1109/TNSRE.2023.3277749 PMID:37200116

Sun, X., Ge, J., Li, L., Zhang, Q., Lin, W., Chen, Y., Wu, P., Yang, L., Zuo, C., & Jiang, J. (2022). Use of deep learning-based radiomics to differentiate Parkinson's disease patients from normal controls: A study based on [(18)F]FDG PET imaging. *European Radiology*, *32*(11), 8008–8018. doi:10.1007/s00330-022-08799-z PMID:35674825

Suri, J. S., Maindarkar, M. A., Paul, S., Ahluwalia, P., Bhagawati, M., Saba, L., Faa, G., Saxena, S., Singh, I. M., Chadha, P. S., Turk, M., Johri, A., Khanna, N. N., Viskovic, K., Mavrogeni, S., Laird, J. R., Miner, M., Sobel, D. W., Balestrieri, A., ... Fouda, M. M. (2022). Deep Learning Paradigm for Cardiovascular Disease/Stroke Risk Stratification in Parkinson's Disease Affected by COVID-19: A Narrative Review. *Diagnostics (Basel)*, *12*(7), 1543. doi:10.3390/diagnostics12071543 PMID:35885449

Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. *Lancet Neurology*, *20*(5), 385–397. doi:10.1016/S1474-4422(21)00030-2 PMID:33894193

Varghese, J. (2020). Artificial Intelligence in Medicine: Chances and Challenges for Wide Clinical Adoption. *Visceral Medicine*, *36*(6), 443–449. doi:10.1159/000511930 PMID:33442551

Vásquez-Correa, J. C., Arias-Vergara, T., Orozco-Arroyave, J. R., Eskofier, B., Klucken, J., & Nöth, E. (2019). Multimodal Assessment of Parkinson's Disease: A Deep Learning Approach. *IEEE Journal of Biomedical and Health Informatics*, *23*(4), 1618–1630. doi:10.1109/JBHI.2018.2866873 PMID:30137018

Xia, Y., Yao, Z., Ye, Q., & Cheng, N. (2020). A Dual-Modal Attention-Enhanced Deep Learning Network for Quantification of Parkinson's Disease Characteristics. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *28*(1), 42–51. doi:10.1109/TNSRE.2019.2946194 PMID:31603824

Xu, W., Chen, L., Cai, G., Gao, M., Chen, Y., Pu, J., Chen, X., Liu, N., Ye, Q., & Qian, K. (2023). Diagnosis of Parkinson's Disease via the Metabolic Fingerprint in Saliva by Deep Learning. *Small Methods*, *7*(7), 2300285. doi:10.1002/smtd.202300285 PMID:37236160

Yoo, H., Chung, S. H., Lee, C. N., & Joo, H. J. (2023). Deep Learning Algorithm of 12-Lead Electrocardiogram for Parkinson Disease Screening. *Journal of Parkinson's Disease*, *13*(1), 71–82. doi:10.3233/JPD-223549 PMID:36641685

Zhang, J. (2022). Mining imaging and clinical data with machine learning approaches for the diagnosis and early detection of Parkinson's disease. *npj. Parkinson's Disease*, *8*(1), 13. PMID:35064123

Zhang, J., Lim, J., Kim, M.-H., Hur, S., & Chung, T.-M. (2023). WM–STGCN: A Novel Spatiotemporal Modeling Method for Parkinsonian Gait Recognition. *Sensors (Basel)*, *23*(10), 4980. doi:10.3390/s23104980 PMID:37430892

KEY TERMS AND DEFINITIONS

CNN: A deep learning approach that is widely used for solving complex problems, and overcomes the limitations of traditional machine learning approaches.

Disability-Adjusted Life Years: A measure for total health combining Years Lost due to Disability and the Years of Life Lost due to premature mortality.

Lewy Bodies: The defining pathological characteristic of Parkinson's disease and dementia with Lewy bodies, constitute the second most common nerve cell pathology, after the neurofibrillary lesions of Alzheimer's disease.

MDS-UPDRS: The most widely used clinical Parkinson's Disease Rating Scale, which consists of four sections, including Non-motor Experience of Daily Life; II: Motor Experience of Daily Life; III: Motor Examination; IV: Motor Complications;

Robustness: The capacity of an analytical procedure to produce unbiased results when small changes in the experimental conditions are made voluntarily.

Substantia Nigra: Is a midbrain dopaminergic nucleus which has a critical role in modulating motor movement and reward functions as part of the basal ganglia circuitry.