

Research on Multi modal Parkinson's Disease Diagnosis System Based on Deep Learning Model

Jiaying Xu¹ Chao Qiu^{*}

¹ Department of Neurology, Tiantai People's Hospital of Zhejiang Province (Tiantai Branch of Zhejiang Provincial People's Hospital), Hangzhou Medical College, Taizhou, Zhejiang, China, Kangning Middle Road 1, Shifeng Street, Tiantai, Zhejiang, P.R. China (317200)

^{*} **Department of Neurology**, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), 54 Youdian Road, Hangzhou, Zhejiang Province, P. R. China

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease caused by reduced dopamine secretion. Deep learning (DL) has received widespread attention in PD diagnosis research, and the number of papers published in this discipline is also increasing. Compared with common machine learning methods, PD detection using DL presents more promising results. This article will review the application of machine learning and deep learning based on multimodal imaging in early diagnosis, classification research, and functional prediction of Parkinson's disease, and explain their limitations, as well as provide prospects for future development trends. To achieve our research objectives, we retrieved and analyzed available research papers from databases such as Scopus, Web of Science, Spring, CNKI, and Wanfang.

Keywords: Deep Learning, Big Data, Parkinson's Disease, Multi modal

Introduction

Parkinson's disease (PD) is a neurological disorder whose etiology has not been fully elucidated and is characterised by chronic, progressive degenerative changes in neurological function [1]. PD is uncommon in people under 50 years of age, and its prevalence climbs with age, peaking between the ages of 85 and 89 years [2]. Approximately 1% of people over the age of 60 will eventually be diagnosed with PD, which could affect 9 million people globally by around 2030 [3, 4]. PD is more common in men than in women, with a male to female ratio of 1.4:1.0. The majority of patients with PD are currently idiopathic and may be affected by genetic effects on the one hand and environmental factors on the other [5]. Epidemiological studies have found that exposure to herbicides, pesticides and heavy metals increases the likelihood of PD, whereas smoking and caffeine use reduce the risk of PD. The medical, social and economic burden of PD is growing rapidly with an ageing population, increased availability of diagnostic tests and improved survival rates due to medical treatments [6]. Damage to dopaminergic neurons is a major pathophysiological alteration in PD, particularly in the ventral-lateral layer of the dense midbrain substantia nigra, which impairs the dopamine transmission pathway in the substantia nigra striata, resulting in a reduction of dopamine levels in the striatum [7]. Lewy bodies are pathological markers of PD and are located within neurons and consist mainly of α -synuclein aggregates.

A widely accepted explanation for the neuropathological progression of PD is the Braak hypothesis model [8], which suggests that PD begins in the medulla oblongata and the olfactory bulb, which is associated with sleep disturbances and olfactory hyperalgesia that may be present in the early stages of the patient's life. Subsequent progression of the pathology to the substantia nigra pars compacta and other midbrain and basal forebrain structures results in the development of typical motor symptoms, and it is at this stage that most PDs are diagnosed. When PD develops into advanced stages, the pathology progresses to the patient's cerebral cortex, which is often accompanied by clinical symptoms such as cognitive deficits or hallucinations [9]. The diagnosis of PD is based on clinical symptoms, and the current diagnostic criteria for motor symptoms include bradykinesia, accompanied by muscle rigidity or resting tremor [10-12]. However, the gold standard for diagnosis remains post-mortem pathological confirmation [13], and based on post-mortem findings, it is believed that approximately 10-20% of patients with a clinical diagnosis of PD are misdiagnosed (Fig.1). Although PD is mainly based on motor symptoms, many patients present with a wide range of other non-motor symptoms, such as autonomic dysfunction, decreased sense of smell, sleep problems, constipation and anxiety. Motor symptoms are a key clinical symptom in PD patients, which have a great impact on daily activities and daily life, and are also an important factor contributing to disability [14]. Schrag and Banks [15] studied 459 PD patients with onset of disease before the age of 65, and found that more than half of them retired early, and the average duration of unemployment was about 4 years, and the average duration of unemployment was about 3 years. The average duration of unemployment due to PD was about 4.9 years. Early diagnosis of PD and tracking of symptom progression is critical to patient treatment planning and outcomes [16-20]. Objective biomarkers to monitor the course of PD are lacking. Currently, pharmacological treatments related to motor symptoms in PD are dominated by dopamine, which is the initial treatment for PD. Anticholinergic drugs are useful in younger patients, especially those with significant hand and foot tremors, but need to be used with caution as some adverse events may occur [21-24]. Choosing the best strategy for initiating treatment for PD may require shared decision-making with the patient to consider benefits and risks. The use of levodopa may result in more functional improvements, but also increases the risk of dyskinesias, especially at high doses of levodopa. Currently, the evidence for treatments for these symptoms in patients with PD varies. Therefore, when developing treatments aimed at slowing the progression of PD, the expectation is that clinical trials will include individuals who are likely to progress more rapidly, so that if a treatment is effective, it can be identified more easily and earlier. Therefore, we hope to find relevant biological markers to predict the rate of disease progression in PD, which will not only help in the design of clinical drug trials, but also help physicians plan disease management and help PD patients understand the impact of the disease on their lives.

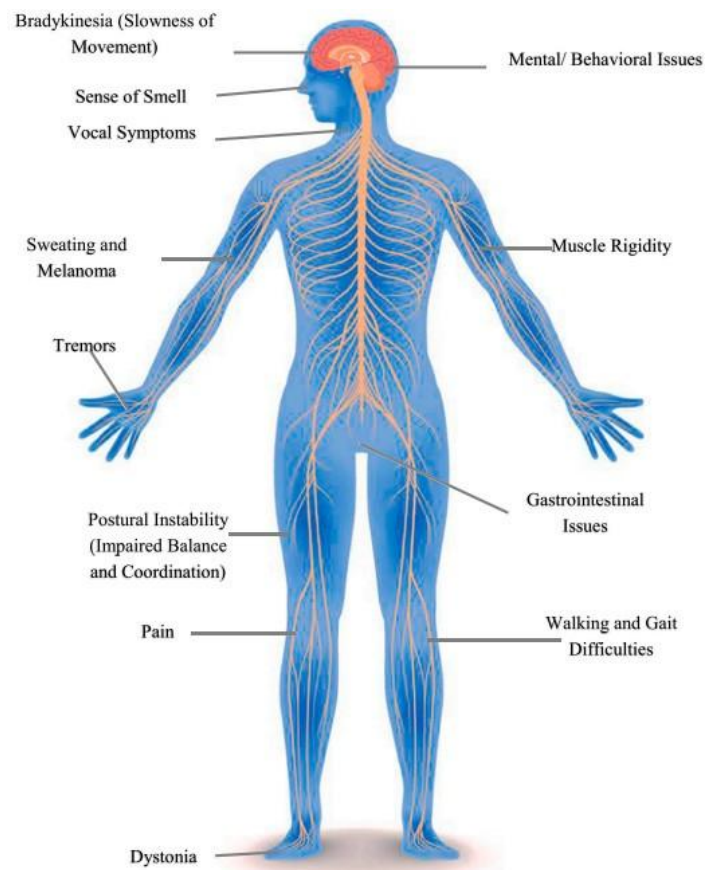


Fig 1. Parkinson's Disease Symptoms

Several studies (**Fig.2**) have utilized data science to participate in the development of medical research considering several aspects such as disease diagnosis and classification [25]. With emerging artificial intelligence methods, software systems can be utilized to present accurate and speedy detection of diseases in the medical sector. Hence, Deep Learning (DL), Machine Learning (ML), and Data Mining (DM) methods have been utilized to select relevant features and cluster them for suitable diagnosis and prediction of diseases [26]. DL generates Artificial Neural Networks (ANNs) [27] that mimic the architecture and operation of the brain in humans. Neural Networks, made up of connected neurons or nodes, are capable of detecting complex relationships and trends in data. DL has been implemented in NLP, autonomous driving, and image/audio recognition. DL can forecast and aid in reaching decisions according to data-driven patterns and relationships, eliminating the need for specific rule-based coding. This renders them especially useful in fields such as medical care, where complicated data can be difficult for individuals to interpret. For effective use of these techniques, large amounts of data and computer resources are required for training and testing processes.

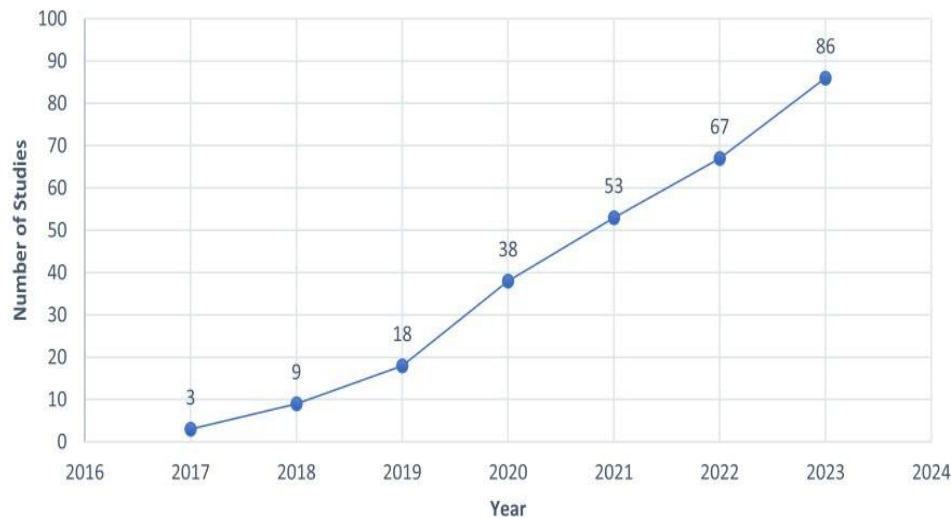


Fig 2. Distribution of Papers per Year.

Deep Learning

Deep Learning specifically refers to machine learning based on deep neural network models and methods. It is developed on the basis of statistical machine learning, artificial neural networks and other algorithmic models, combined with the contemporary development of big data and big computing power. The most important technical feature of deep learning is the ability to automatically extract features, and the extracted features are also called deep features or deep feature representations, which are stronger and more robust than manually designed features [28]. Therefore, the essence of deep learning is feature representation learning. Deep neural networks are the model basis for deep learning to be able to extract features automatically, and deep neural networks are essentially a series of nested nonlinear transformations. At present, it seems that deep learning is the most promising technical way to solve the major scientific and technological problem of strong artificial intelligence, and it is also the current research hotspot in the field of computer, big data science and artificial intelligence. Deep learning is an interdisciplinary technical field involving data science, statistics, engineering science, artificial intelligence and neurobiology, and is an important branch of machine learning.

Deep learning is a subfield of machine learning and is a supervised machine learning approach using a specific architecture, whose strength lies in its scalability, which largely depends on the ability to automatically extract relevant features [29-31]. Deep learning consists of CNN (**Fig.3**), transfer learning and generative adversarial networks. CNN evolved from multilayer perceptrons [32]. CNN have multiple layers of convolution and activation to form an efficient representation of the input data [33]. Relocation learning is a deep learning method that transfers knowledge from one domain (source domain) to another domain (target domain)

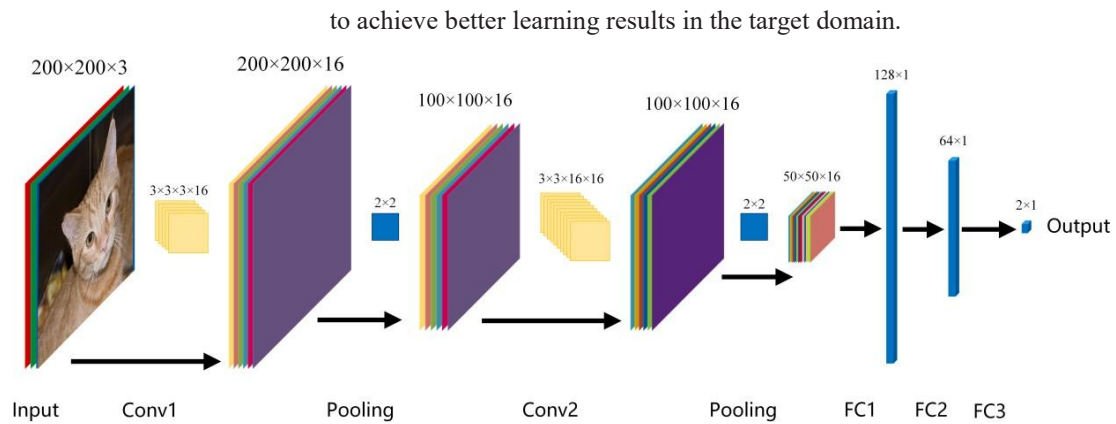


Fig 3. CNN model

Imaging of Gait Disorders in Parkinson's Disease

Structural imaging techniques

Magnetic resonance (MR) based techniques provide methods to visualise the microstructural anatomy of brain tissue. Voxel-based morphometry (VBM) is a technical approach using high-resolution 3D T1-weighted imaging that allows direct comparison of local grey matter volumes between subjects [34]. Other structural imaging techniques include diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI), which is a method for detecting the diffuse movement of water molecules within the brain, and DTI, which is a visualisation tool and method based on DWI. DTI is a visualisation tool and method based on DWI that allows quantitative analysis of the diffusive movement of these water molecules. Alterations in brain structure have been shown to correlate with the risk or degree of gait dysfunction in Parkinson's disease, and the motor subtypes of PD include tremor dominate (TD) and PIGD, which are often indicative of different pathophysiological changes [35-37]. Following the findings that patients with TD have less grey matter (GM) atrophy in the frontal, parietal, occipital and temporal lobes, as well as in the caudate nucleus and cerebellar vertices, than those with PIGD. Rosenberg-Katz et al. [38] found that patients with TD had a larger GM volume (GMV) in the amygdala and the pallidum, but a larger GMV in the amygdala and the pallidum. Later, Rosenberg-Katz et al. found greater GMV in the amygdala and pallidum in patients with TD, but not in the cerebellar region, and in 2017, a group of researchers found that although GMV in the frontal cortex was lower in TD patients than in PIGD patients, this difference disappeared significantly when the severity of the disease, the time of evolution of the disease, and the use of medications were taken into account [39]. GM atrophy in frontal regions may be a potential cause or consequence of cognitive decline in PD. Cognitive decline is common in patients with PIGD [40], and cognitive decline itself may contribute to gait difficulties, as the risk of falls in patients with PD has been found to be associated with a bidirectional motor-cognitive

dependence on executive function. Changes in the GMV of the amygdala may underlie many of the emotional problems of PIGD patients, such as depression, apathy and anxiety. Recent studies have found that anxiety and depression may also affect the patient's gait. In the later stages of PD, FOG occurs more often, is often difficult to treat, and results in a significant reduction in the patient's quality of life. Snijders et al. ^[41] focused on the relationship between the Mesencephalic locomotor region (MLR) and FOG, using VBM as well as quantitative measures of the region of interest, and found that FOG was associated with the absence of FOG. Using VBM and quantitative region of interest measurements, they found that a portion of the GM in the MLR was more severely atrophied in PD-FOG patients compared to PD patients without FOG (PD-nFOG) and healthy subjects. Sunwoo et al ^[42] also analysed subcortical brain structures and found that the thalamus volume was smaller in patients with PD-FOG than in patients with PD-nFOG. Finally, Herman et al ^[43] demonstrated that there was a significant loss of GM in the caudate nucleus bilaterally in PD-FOG compared to PD-nFOG. It has also been found that GMV alterations in PD-FOG are in cortical rather than subcortical structures by VBM methods ^[44].

Functional Imaging

Functional magnetic resonance imaging (fMRI) is a key brain imaging technique that monitors changes in blood oxygenation level dependent (BOLD) blood flow related to brain activity, thereby reflecting brain activity. BOLD-fMRI is a key brain imaging technique. BOLD- fMRI acquisition modalities are divided into task-based fMRI (tb-fMRI) and resting-state fMRI (rs-fMRI). tb-fMRI is a technique that measures neural activity by determining changes in blood oxygenation level-dependent functional magnetic resonance imaging (MRI) signals during the performance of a specific task ^[45]. tb-fMRI is a technique that measures neural activity by determining changes in blood oxygen level-dependent functional magnetic resonance imaging signals during the performance of a specific task. rs-fMRI is a technique that measures interactions between regions of the brain in the resting state, and common analyses include the Regional homogeneity (ReHo) analysis, the Amplitude of low frequency fluctuation (ALFF), and the Amplitude of low frequency fluctuation (ALFF), which is a measure of neuronal activity. Common analysis methods include ReHo, Amplitude of low frequency fluctuation (ALFF), and Functional connectivity (FC), etc. ReHo is often used to depict the synchronous movement of neurons associated with neighbouring brain regions, ALFF is often used to describe the strength of neuronal activity associated with a specific brain region, and FC represents the synchronicity of BOLD signal changes associated with two different brain regions. ReHo mainly analyses changes in brain activity in local brain regions, as does ALFF ^[46]. Previous studies have shown that motor imagery tasks activate neural processes that resemble real motor behaviour, including gait ^[47]. A number of studies have shown that tb-fMRI changes between PIGD and TD patients are mainly in the

cerebellum, nucleus accumbens, temporal cortex, and parietal cortex [48]. Many other researchers have investigated the pathophysiological process of FOG in PD patients by tb-fMRI and motor imagery modalities [49].

Functional nuclear medicine tomography technology can study the changes in walking function abnormalities in PD patients at the molecular level. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are two commonly used nuclear medicine imaging techniques for studying PD. The principle of most PD related molecular imaging techniques is mainly related to the absence of dopamine transporters on the presynaptic membrane of dopaminergic nerve endings in the substantia nigra striatum. Most PET studies use 18F-FP-CIT as a radioligand for dopamine receptors and reabsorption sites because compared to other radioligands, it has fast kinetics, relatively long half-life, and lower radiation exposure. Researchers compared PET scans of PIGD and TD patients and found that dopamine uptake in the caudate nucleus and putamen was significantly reduced in PIGD patients, which may indicate that PD patients with gait disorders have a worse prognosis [50]. In addition, PET related studies have consistently found that dopamine activity in the striatum of PD-FOG patients is lower than that of PD nFOG patients, mainly involving brain regions such as the right putamen and caudate nucleus [51]. In SPECT studies related to PD, 123I-FP-CIT imaging agents are often used to track dopamine uptake in the striatum. When studying dopamine transporter activity using SPECT, it was found that lower levels of dopamine transporter activity in the striatum can significantly predict the occurrence of FOG in PD patients [52].

Early diagnosis of PD based on neuroimaging biomarkers

Early diagnosis of PD based on brain structural imaging

VBM is a technique for analyzing brain MRI images at the voxel level, which can display changes in local gray matter, white matter density, and volume, and is widely used in PD research [53]. Takahashi et al. [54] used quantitative magnetic susceptibility mapping (QSM) and neuromelanin imaging to evaluate Parkinson's disease (PD), proposed an automatic region of interest (ROI) selection method for VBM, and obtained QSM values and neuromelanin values of the substantia nigra pars compacta. The results showed that the QSM values of the PD group were significantly higher than those of the healthy controls (HC) group, while the neuromelanin values of the PD group were significantly lower than those of the HC group. Peng et al. [55] used multi-level ROI features to detect sensitive morphometric biomarkers in PD, integrating low-level ROI features (gray matter volume, cortical thickness, etc.) and high-level correlation features (connectivity between ROIs) to construct multi-level ROI features (Fig.4). The classification algorithm based on feature selection and multi-core support vector machine performed well in PD and HC classification, with an accuracy of 85% 78% with a specificity of 87 79%, with a sensitivity of 87 64%. Different from

the study of morphological differences between gray and white matter, diffusion tensor imaging (DTI) can measure the random movement of water molecules in tissues along a specified direction. It is a non-invasive method for characterizing the microstructure of tissues and is currently widely used in the research of neurodegenerative diseases [56]. Ramirez et al. [57] developed and evaluated an autoencoder model to extract the average diffusion coefficient and local anisotropy score from whole brain DTI data. The ability to distinguish between HC and PD patients was measured based on the intensity and localization of voxel reconstruction errors in the images. The ROC curve was used as a performance measure for classification problems, and it was found that the structures with higher AUC were the combination of substantia nigra, red nucleus, thalamus, and all subcortical structures.

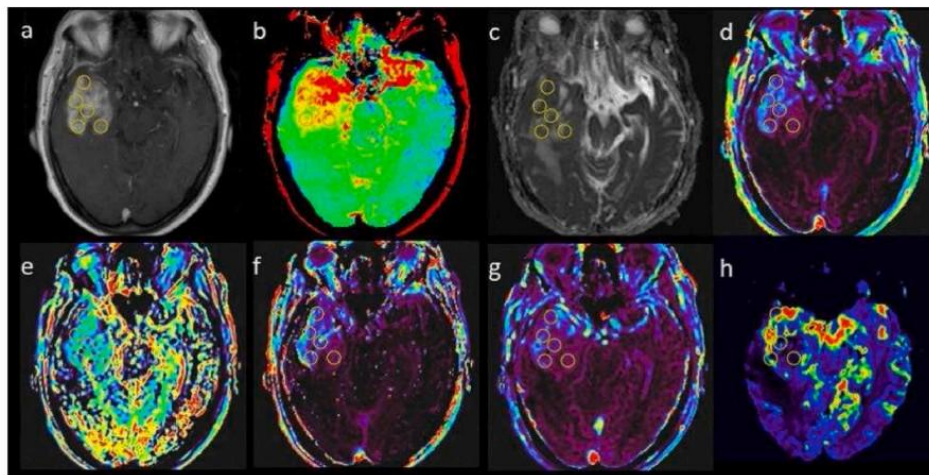


Fig 4. Region-of-interest (ROI) measurements in a 68-year-old female with glioblastoma. Round ROIs with a diameter of 10 mm are placed to fill the solid enhancing part of the tumor on contrast-enhanced T1-weighted image (a). The ROIs were copied onto maps of APTSI (b), ADC (c), Ktrans (d), kep (e), ve (f), vp (g), and rCBV (h) [58]

Early diagnosis based on lesions in the brain

PET and SPECT imaging have been used extensively in the diagnosis of neurodegenerative diseases, and have become objective tools for the early detection of dopamine degeneration and the measurement of the rate of progression of the PD process. The loss of dopamine neurons is mainly concentrated in the caudal and lateral regions of the substantia nigra compacta, in which the nigrosome -1 region (N1) is a potential imaging biomarker for pathophysiological changes in PD patients. Shin et al. [59] used a region-based object detection method and the CNN model YOLOv3 to detect and accurately classify abnormalities in the N1 region, and the results demonstrated that it is feasible to identify and evaluate the N1 region on magnetic susceptibility-weighted MRI, and the diagnostic performance is very high. Piccardo et al. [60] conducted the first AI-based study to identify the effects of nigrostriatal degeneration in patients with 18 F -DOPA PET/CT, and tested the diagnostic accuracy of a 3D CNN model in identifying pa-

tients with presynaptic dopamine deficits, and found that the model had very high sensitivity and specificity. In addition to early diagnosis of PD based on substantia nigra striata degeneration, MRI data can also be used to observe other brain regions affected by this disease. Sateesh et al. ^[61] proposed a metacognitive radial basis function network (McRBFN) classifier based on recursive feature elimination from MRI to identify the key brain regions of PD. The McRBFN classifier extracts voxel based morphometric (VBM) features from MRI and adopts a projection based learning (PBL) algorithm. The results show that the PBL-McRBFN classifier has good generalisation performance for PD prediction, and the features selected by PBL-McRBFN-RFE suggest that the absence of grey matter in the superior temporal gyrus may be the cause of PD. Esmailzadeh et al ^[62] used CNNs based on 3D MRI images and also used patient's age and gender features for training, and found that 100% accuracy was achieved on both validation and test sets, and the brain thermograms created for the diagnosis of PD revealed for the first time that the right supratentorial portion of the brain is also very important in the diagnosis of PD.

Prognostic prediction of motor and cognitive function in PD

In addition to the early diagnosis and classification of PD, scholars have conducted tracking and prediction studies on the motor function of PD. In addition to the early diagnosis and classification of PD, scholars have conducted tracking and prediction studies on motor function in PD. DAT - SPECT has been widely used in PD research, and the quantitative analysis of DAT images using radiological features and non-imaging features can predict the prognosis of patients. Adams et al. ^[63] used part III of the unified Parkinson's disease rating scale (UPDRSIII) score at baseline and the complete DAT images to predict patients' UPDRSIII score at year 4 by CNN without extracting features, and compared the predicted score with the patients' UPDRSIII score at year 4. A 10-fold cross-validation was performed between the predicted score and the actual UPDRS III score of the patient at year 4, and the average accuracy of all cross-validations reached $70.7\% \pm 7.7\%$, which demonstrated the feasibility of applying CNNs to image and non-imaging features for clinical prediction. Salmanpour et al. ^[64] used machine learning to predict the prognosis of motor and cognitive functions in Parkinson's disease. After analysing 18 patient features (clinical features: UPDRS I, II, and III scores, age, gender, and duration of the disease in year 0 and year 1; and DAT-SPECT imaging features: uptake of the nucleus accumbens and caudate nucleus in year 0 and year 1), 32 feature combinations were created. Using a local linear model tree and a feature subset selector algorithm, the actual UPDRS III scores at year 4 were used as the predictor of outcome, resulting in the UPDRS III scores at year 0 and year 1 being highly significant predictors of motor symptom severity at year 4, and the Montreal Cognitive Assessment Scale (MCAS) at baseline and year 1 being used as the best predictor of motor symptom severity at year 4 using the optimisation tool, the feature subset selector al-

gorithm, and various prediction algorithms. At the same time, optimisation tools, feature subset selector algorithms and optimal use of various prediction algorithms based on baseline levels and the Montreal Cognitive Assessment Scale at year 1 can produce very good predictions of cognitive outcomes ^[65]. Deep brain stimulation is a surgical treatment for PD that can improve motor symptoms in patients with PD, but the treatment effect is still highly variable, so it is important for preoperative decision-making and prediction of postoperative motor status. Liu et al. ^[66] constructed an imaging histology combined with machine learning prediction model based on the imaging histological features of the substantia nigra in preoperative QSM images of patients, and found that it had a better prediction performance on the overall movement and motor stiffness of postoperative patients, and was better than that of the conventional model of the response to preoperative levodopa stimulation test, which indicated that this prediction model is an innovative and practical method to assist clinicians in their preoperative decision-making.

Conclusion

PD has become a chronic disease that cannot be ignored in the future after diabetes and hypertension. Deep learning, as one of the methods to realise artificial intelligence, can diagnose PD more objectively and accurately than traditional scales, which can help doctors to provide targeted treatment for PD, but its diagnosis is also limited by the lack of effective biomarkers, small medical data sets, low reproducibility, and difficult to be interpreted. In the future, artificial intelligence can be used to increase the sample size of the study by collaborative analysis of data from multiple sites. On this basis, the machine learning result-oriented differential diagnosis of PD will, to a certain extent, fill the gaps in the traditional PD diagnosis, which is of great significance to the accurate diagnosis, rehabilitation treatment, and efficacy evaluation of PD patients. Classification features with the highest relevance to PD need to be extracted from the high-dimensional neuroimaging data, and the multimodal image features should be effectively fused through feature selection and the addition of clinical data to improve the classification model.

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