Long-Term Cognitive Prediction in Parkinson's Disease Based on Clinical Features and Deformation Morphometry

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Abstract

Parkinson's disease (PD) is a progressive disorder. In this study, we proposed a deep learning model that utilized participants' baseline clinical features and deformation-based morphometry (DBM) to predict long-term cognitive trajectory over four years. A total of 216 participants from the PPMI (Parkinson's Progression Markers Initiative) dataset were included, with 157 being PD patients and 59 healthy controls. We identified brain connectivity patterns associated with long-term cognitive decline using DBM and independent component analysis (ICA) techniques. Results of the cognitive prediction indicated that using only clinical features, DBM features, and multimodal features yielded average accuracies of 76 ± 4%, 70 ± 6%, and 78 ± 2%, and average AUC (Area Under the Curve) of 0.71 ± 0.06, 0.62 ± 0.04, and 0.76 ± 0.06, respectively. Our study demonstrated that the potential of using DBM features to better predict disease progression.

1. Introduction

Parkinson's disease ranks as the second most prevalent neurodegenerative disorder. PD symptoms primarily include motor dysfunctions such as bradykinesia, tremor, and postural instability, often accompanied by non-motor symptoms such as sleep disturbances, depression, olfactory deficits, and memory impairment. Currently, there is no cure for PD, and clinical treatments, including levodopa, dopamine agonists, or deep brain stimulation, only alleviate symptoms. Therefore, predicting the progression of PD is crucial for personalized patient care.

The MoCA score is extensively utilized to assess cognitive impairment (CI) in PD patients, as it encompasses a range of common non-motor symptoms. The MoCA has a total score of 30, with a cutoff value of 26. Patients scoring below 26 are considered to have varying degrees of cognitive impairment [1]. Research indicated that the risk of dementia in PD patients increased after four years. Therefore, this study aimed to predict long term cognition (based on MoCA scores) in patients four years later using their baseline characteristics. In this study, we propose a method that uses clinical features and DBM to predict the four-year cognitive trajectories of Parkinson's patients and healthy controls. The contributions of this study are as follows:

1) We defined a trajectory model based on participants' long-term MoCA scores, which allowed for trajectory estimation even in the presence of missing data for any given year.
2) We used DBM and ICA to identify brain connectivity patterns associated with long-term cognitive decline, and employed multimodal methods to predict disease progression.

2. Related work

MRI and SPECT are the most common neuroimaging techniques used in Parkinson's disease. Researchers often use deep learning networks to process MRI images; however, deep learning is better suited for complex predictive tasks and its "black box" nature and high computational demands may make it less effective than DBM for morphological analysis and interpretation. DBM can identify overlapping regions of atrophy and intrinsic connectivity networks. Therefore, we used DBM and tensor-based probabilistic ICA to identify brain atrophy and predict PD progression.

In recent years, many researchers have analyzed the relationship between DBM and various symptoms of PD, but few have used DBM to predict PD progression. For example, Rosinvil et al. [2] employed DBM to examine neuroanatomical substrates and found that excessive daytime sleepiness correlated with higher doses of dopamine receptor agonists, more severe motor symptoms, and specific neuroanatomical changes such as increased surface area in the right insula and contracted surfaces in the right putamen and amygdala. Wang et al. [3] employed DBM and hierarchical clustering to identify two neuroanatomic biotypes in newly diagnosed PD, revealing distinct differences in subcortical brain volumes and clinical severity. They found that patients with smaller subcortical volumes had more severe motor impairments and a faster decline in clinical symptoms and dopamine functional imaging over five years. Pieperhoff et al. [4] used DBM to analyze longitudinal MRI and tracked regional brain atrophy over up to 8.8 years. It indicated that PD patients exhibited accelerated volume loss primarily in the occipital and temporal lobes, as well as in the insula and putamen, which correlated with worsening clinical symptoms. Such studies have not further leveraged the advantages of DBM to predict disease progression.

3. Proposed method

We proposed a multimodal approach to predict participants' long-term cognitive trajectories. First, the DBM

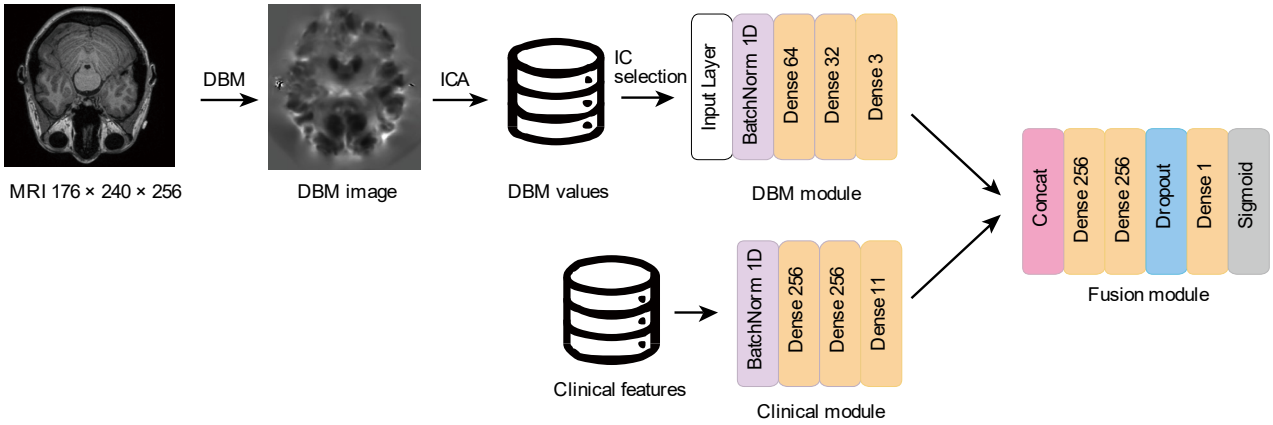

Fig. 1 Proposed multimodal model for predicting long-term cognitive decline in Parkinson's disease.

module processed the raw 3D MRI images to obtain DBM images, which were then subjected to independent component analysis. Pearson correlation coefficients were used to select the independent components. These selected components, along with clinical features, were fed into the MLP networks to predict the subtype of cognitive trajectory over the four-year period, as shown in Fig. 1.

A. Deformation-Based Morphometry

We used DBM to assess local changes in tissue density by non-linearly transforming MRI images to a stereotaxic template and measuring tissue deformation. DBM was preferred over Voxel-Based Morphometry (VBM) because VBM does not preserve the entirety of MRI data and may be less sensitive to subcortical atrophy. For DBM, we registered each brain non-linearly to the MNI152-2009c template, pre-processing the MRI images with denoising, intensity correction, and linear intensity scaling, as described in [6]. We then computed voxel displacements to create a map showing how each voxel was adjusted to fit the template. To estimate local atrophy, we calculated the determinant of the local Jacobian matrix of displacement.

B. Independent Component Analysis and Component Selection

To ensure comparability between groups, we concatenated all participants' DBM maps obtained in the previous step into a 4D image for ICA. ICA is a method that decomposes data into independent components without prior knowledge [7]. We used the GIFT toolbox in MATLAB to perform ICA with the number of components set to 30 and the Infomax algorithm. Given ICA's inherent randomness, we ran the Infomax algorithm 10 times using ICASSO to assess its stability and reliability. Finally, the independent component maps were converted to Z-statistical images with a threshold of $Z > 3$.

ICA also produced a spatial component matrix with the size of $P \times C$, where P was the number of participants and C was the number of independent components. This matrix represents the intensity or activation level of each independent component for each participant. Due to noise and instability in the ICA process, as well as the presence of components with no significant association with clinical data, we computed the Pearson correlation coefficient between each ICA component and participants' labels, and assessed significance using t-test p-values. The independent components significantly associated with the labels were ultimately identified.

4. Results and Discussion

A. Dataset, participants and labelling result

We aimed for the labels to reflect participants' long-term cognitive types. To achieve this, we employed the method proposed by Bhagwat et al. [5], classifying participants' long-term cognitive trajectories based on MoCA scores from baseline to the fourth year. Euclidean distance was used as the similarity measure between longitudinal MoCA scores, and clustering was performed using the Ward method. Trajectories were created under the condition of having at least three years of follow-up data; thus, participants with two years or fewer of follow-up were excluded from the study.

We obtained 157 PD patients and 59 healthy controls from the PPMI dataset. PPMI was launched in 2010 to identify biomarkers for Parkinson's disease progression. The participants in our study were enrolled between July 2010 and May 2023. Finally, out of 216 participants, we classified 149 as cognitively stable and 67 as exhibiting cognitive decline over four years. Fig. 2 illustrates the cognitive trends for these two trajectories, as determined by 5-fold cross-validation. We found that Trajectory 1 had higher MoCA scores at baseline, with scores remaining relatively stable over the four-year period. In contrast, Trajectory 2 exhibited markedly different results, with baseline MoCA scores around 26 and a significant decline in the first year.

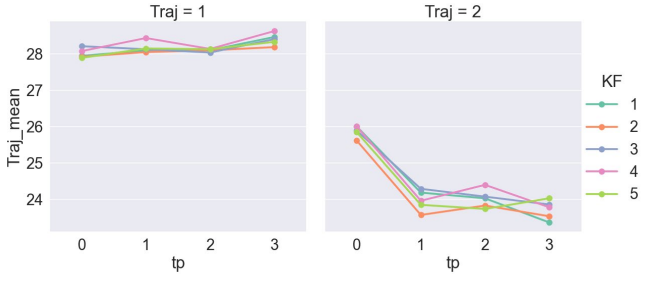

Fig. 2 Trends in MoCA scores for the two trajectories over four years.

B. *Clinical features selection*

As described in existing researches [8], [9], the predictors in Table I are strongly associated with the MoCA scores. Therefore, those predictors were included as the inputs of the clinical module.

Table I Selected baseline clinical features for long-term cognitive prediction.

Clinical Features	HC (n=59)		PD (n=157)	
	Mean	(SD)	Mean	(SD)
Demographic				
Age	61.1	(10.1)	61.6	(9.3)
Sex (male/female)	38/21		103/54	
Education (years)	15.6	(2.8)	15.5	(2.8)
Clinical characteristics				
MoCA	28.2	(1.1)	27.5	(2.0)
UPSIT	33.2	(4.8)	22.3	(8.8)
STAI	56.9	(14.1)	65.9	(18.3)
HVLT Discrimination	9.7	(3.2)	9.7	(2.6)
LNS	11.1	(2.3)	10.8	(2.8)
QUIP	0.5	(1.0)	0.3	(0.6)
SCOPA	6.1	(3.7)	9.4	(6.4)
GDS	1.5	(2.9)	2.5	(2.6)

SD, Standard Deviation; STAI, State-Trait Anxiety Inventory; HVLT Discrimination, Hopkins Verbal Learning Test Discrimination Index; LNS, Letter-Number Sequencing; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; SCOPA, Scales for Outcomes in Parkinson's Disease; GDS, Geriatric Depression Scale.

C. *Pearson correlation and spatial maps of independent components*

Table II lists the p-values for all 30 independent components obtained from Pearson correlation analysis. Participants with long-term decline cognitive showed significantly decreased integrity in IC7 (0.0005), IC9 (0.007) and IC15 (0.049) compared to participants with long-term stable cognitive.

Table II p-values from the t-test based on Pearson correlation coefficients.

IC1	IC2	IC3	IC4	IC5	IC6
0.36	0.94	0.52	0.47	0.59	0.92
IC7	IC8	**IC9**	IC10	IC11	IC12
0.0005	0.80	**0.007**	0.29	0.23	0.27
IC13	IC14	**IC15**	IC16	IC17	IC18
0.88	0.23	**0.049**	0.32	0.32	0.34
IC19	IC20	IC21	IC22	IC23	IC24
0.49	0.97	0.66	0.47	0.92	0.72
IC25	IC26	IC27	IC28	IC29	IC30
0.13	0.45	0.58	0.79	0.33	0.22

We mapped these three independent components to the atlase of [10] (Fig. 3): IC7 prominently features the caudate nucleus, thalamus, and midbrain, highlighting its role in motor and sensory processing networks; IC9 shows strong associations with motor functions, evident in the cerebellum, and visual processing, indicated by the occipital lobe; IC15 focuses on cognitive, sensorimotor, and emotional processing. The prefrontal cortex's activation is linked to complex cognitive functions, while the involvement of sensorimotor and midline structures reflects integration of sensory inputs, motor coordination, and emotional regulation.

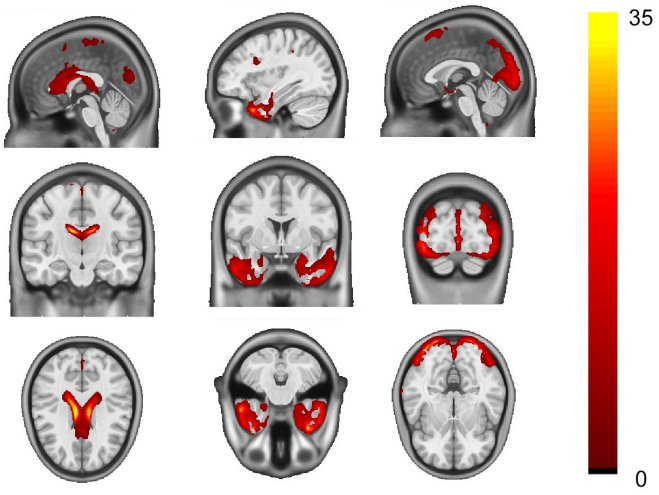

Fig. 3 Spatial maps of independent components. Left: IC7 at voxel 97, 116, 101; Middle: IC9 at voxel 63, 135, 44; Right: IC15 at voxel 97, 43, 75. IC, Independent Component.

D. *Model performance*

The data was divided into two parts, with 85% used for 5-fold cross-validation to select the best model based on the highest F1 score, and the remaining 15% used for testing. In addition to the model shown in Fig. 1, we developed the other two models to compare the testing results with those of the multimodal model: using only 11 clinical features and using only DBM features. Unlike the multimodal model, these models excluded the concatenation and two fully connected layers in the fusion module but retained the dropout, the final fully connected layer, and the sigmoid function.

Table III compares the prediction results of two models after 5-fold cross-validation. When using only clinical data and DBM images, the testing accuracy was suboptimal. The multimodal model achieved the highest mean accuracy (78 ± 2%) and F1-score (0.56 ± 0.04) with the lowest standard deviation, indicating the best robustness in 5-fold cross validation. The performance of models using only clinical features was slightly inferior to those using all modalities, highlighting the significance of clinical features in predictive tasks.

Table III Mean testing accuracy, AUC and F1-score.

Model	Accuracy (%)	AUC	F1-score
Clinical only	76 ± 4	0.71 ± 0.06	0.50 ± 0.09
DBM only	70 ± 6	0.62 ± 0.04	0.40 ± 0.15
Multimodal	78 ± 2	0.76 ± 0.06	0.56 ± 0.04

Fig. 4 visualizes the performance of multimodal model in predicting long-term cognition, with the AUC representing the measure of the model's ability to distinguish between two classes. Consistent with the results in Table III, incorporating clinical features or DBM features increased the AUC values. With an AUC of 0.62, the DBM model had the lowest

performance among the three models. It indicated that while DBM features provided valuable information, it might not be sufficient on its own for accurate predictions. The multimodal model achieved an AUC of 0.76 on the ROC curve. At the selected threshold, the model demonstrated a specificity of 88%, a recall of 51%, and a precision of 64%.

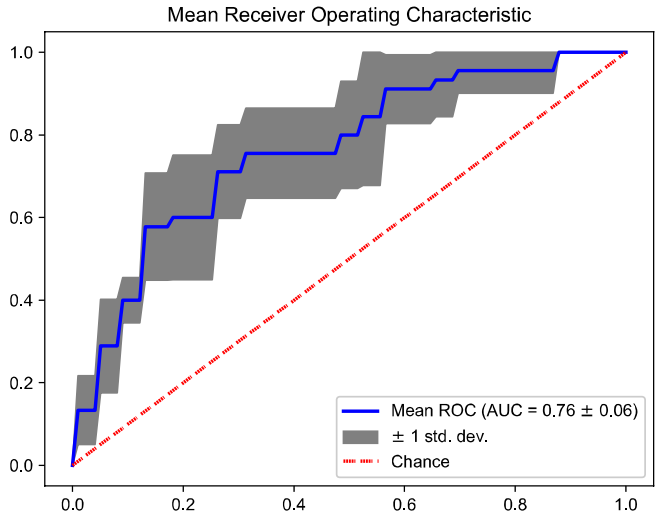

Fig. 4 Mean ROC curve of the multimodal model.

5. Conclusion

In this study, we proposed a deep learning model that leverages baseline clinical and DBM features to predict the long-term cognitive trajectory of PD over four years. Using DBM and independent component analysis (ICA) techniques, we identified brain connectivity patterns associated with long-term cognitive decline. Our cognitive prediction results showed that the average accuracies for using clinical features only, DBM features only, and multimodal features were 76 ± 4%, 70 ± 6%, and 78 ± 2%, respectively. The average AUC values were 0.71 ± 0.06, 0.62 ± 0.04, and 0.76 ± 0.06, respectively. These findings demonstrated that DBM features offer significant potential for improving disease progression prediction, highlighting the added value of integrating DBM with clinical features to enhance predictive accuracy.

However, there are some limitations to this study. After removing participants who could not be labeled, lacked clinical data, or did not have MRI images, only 216 participants met the criteria. This led to an imbalance between the two subtypes, which indirectly resulted in lower F1 scores. Additionally, while we validated the feasibility of the trajectory method and multimodal prediction, the accuracy remained insufficient. Future work could explore incorporating additional clinical data to define trajectories and further refine machine learning methods to improve the applicability of DBM-based MRI processing techniques.

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