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# Morphological changes in Parkinson's disease based on magnetic resonance imaging: A mini-review of subcortical structures segmentation and shape analysis

Deng JH *et al.* Morphological changes in PD based on MRI

Jin-Huan Deng, Han-Wen Zhang, Xiao-Lei Liu, Hua-Zhen Deng, Fan Lin

## Abstract

<sup>2</sup> Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

**Key Words:** Parkinson's disease; Dopaminergic neurons; Magnetic resonance imaging; Substantia nigra; Morphological

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**Core Tip:** Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is primarily caused by the loss of dopaminergic neurons in the substantia nigra. The classical clinical symptoms of PD include movement symptoms such as bradykinesia, resting tremor, rigidity, and postural instability. Recent studies have shown that symptoms of PD extend beyond motricity and include cognitive and neuropsychiatric symptoms. Non-motor symptoms can be identified at all stages, even before the appearance of motor symptoms<sup>[1]</sup>. In addition to clinical markers, PD biomarkers include neuroimaging, genetic, and biochemical markers<sup>[2]</sup>. This review focuses primarily on the use of neuroimaging in PD.

The main pathological features of PD are the degeneration of dopaminergic neurons in the substantia nigra and deposition of Lewy bodies, leading to pathophysiological changes in the downstream basal ganglia circuits. The basal ganglia system includes the striatum, globus pallidus, and structures with functional connections to the striatum, including the subthalamic nucleus, substantia nigra, and red nucleus.

Magnetic resonance imaging (MRI) is one of the most useful noninvasive techniques for examining intracranial structures, showing macroscopic alterations of the subcortical structures, and can visualize their volume and surface morphology. Therefore, MRI-based morphological analysis of the subcortical structures has the potential to be a prominent diagnostic neuroimaging marker for PD. This review focuses on the shape analysis of the striatum, thalamus, and hippocampus, which has been mostly discussed in previous studies.

## **METHODS**

A literature search was conducted<sup>12</sup> for relevant studies using four databases: PubMed, Web of Science, Google Scholar, and Scopus. The key search terms in the different combinations were “Parkinson’s disease, shape analysis, subcortical structures, striatum, thalamus, and hippocampus.” The final search was conducted on October 25, 2022.

The inclusion criteria were the studies that included: (1) A background or introduction on PD; (2) the clinical criteria of PD; (3) an introduction to methods of the subcortical structure segmentation; (4) shape analysis of the subcortical or cortical structures; and (5) data utilization of structural MRI sequences.

We excluded studies<sup>9</sup> based on the following exclusion criteria: (1) Articles published in languages other than English; (2) animal model or theoretical articles; (3) studies with a sample size of < 10 patients; (4) studies whose methodology did not involve volumetric or shape analysis; and (5) review or meta-analysis articles of shape analysis.

## **RESULTS**

Figure 1 shows a flowchart of the study selection. This review included 67 references, of which 2 provided a background/introduction on PD, 5 referred to the segmentation methods, and 60 to the morphology of the subcortical or cortical structures in PD. Subcortical structures mainly included the striatum, thalamus, and hippocampus. Further information on the structures and morphological changes is provided in Table 1.

### *Parkinson's disease*

The Movement Disorders Society (MDS) has proposed the main diagnostic criteria for PD in clinical settings<sup>[3]</sup>. The recent version of the MDS diagnostic criteria considers three stages in the progression of PD: Preclinical, prodromal, and clinical. Clinical PD can be diagnosed when typical motor symptoms occur. Neurodegeneration may occur in patients with PD before they reach the clinical stage<sup>[3]</sup>. Previous studies have been mostly conducted based on clinical diagnosis; therefore, this review focuses on PD in the clinical stage. The striatum is one of the most affected structures in the nigrostriatal pathway because of the **degeneration of dopaminergic neurons**. In addition to **the striatum**, neurons in **the** substantia nigra project to other basal nuclei, such as the pallidum, substantia nigra, and thalamic nucleus basalis. A decrease in dopamine levels may cause the structural and morphological changes observed in PD.

MRI allows noninvasive observation of morphological changes in the subcortical structures in patients with PD to find changes in neuroimaging characteristics. Hence, it may help in clinical intervention, especially in the preclinical or prodromal stages of the disease. However, the naked eye cannot identify subtle changes in structures; hence, quantitative analysis using a computer may help determine the presence or absence of morphological changes in these structures. Segmentation of subcortical structures based on

the images is the prerequisite to performing an accurate analysis. The following sections describe the common segmentation methods and the results of morphological analyses of the subcortical structures obtained from previous studies.

### *Methods of segmentation*

Both manual and automatic segmentation have been used in recent studies. Manual segmentation, usually the gold-standard approach for automatic segmentation, is a tedious and time-consuming task that depends on the subjectivity of the physician. Therefore, many investigators have used publicly available automated segmentation software for efficiency and objectivity. Automatic segmentation methods include voxel-based morphometry (VBM) and surface-based morphometry (SBM). The tools used for segmentation in most studies include FSL and FreeSurfer, among others. The first software, distributed with the FSL package, is a tool that employs manually labeled image data to offer anatomical training information for 15 different subcortical regions using 336 manually labeled T1-weighted MRI images<sup>[4]</sup>. FreeSurfer is a suite of tools for extensive automated analysis of key features in the human brain that can be used in most MRI sequences and provides an accurate geometric surface model<sup>[5]</sup>. By minimizing the difference between the original image and the converted target image, large deformation diffeomorphic metric mapping (LDDMM) creates a differential homogenous transformation that has its own inherent smoothness and simulated displacement size. It is often applied in the object-matching segment of medical imaging data processing<sup>[6]</sup>. This review focuses on the morphological analysis of subcortical structures in PD using the techniques mentioned above in recent years.

Several scholars have compared the effects of manual and automatic segmentation. For the hippocampus and amygdala, segmentation using VBM and FreeSurfer is performed at a level comparable to manual segmentation<sup>[7]</sup>. In another study, automated segmentation revealed different degrees of variability in the subcortical structures compared to manual segmentation, with particularly pronounced differences found in the FreeSurfer and FSL pipelines for the pallidum and thalamus<sup>[8]</sup>. From these studies, it can be seen that the efficiency of automatic segmentation is comparable to that of manual segmentation. Automatic methods save more time and display better segmentation results, which could be used in the shape analysis of the subcortical structures in patients with PD.

#### *Shape analysis of the striatum*

<sup>10</sup> The striatum is a critical component of the brain that controls the motor, reward, and executive functions, and dopamine serves as an important mediator<sup>[9]</sup>. Decreased dopamine levels have the greatest impact on striatal structures in patients with PD. Several studies have segmented the striatum by manual segmentation of T1-weighted MRI images for its morphology, showing that the volume of the caudate nucleus or putamen was smaller in patients than in normal controls<sup>[10,11]</sup>. In addition, studies using automatic segmentation showed the same results as those using manual segmentation of the volume of the caudate nucleus and putamen<sup>[12-17]</sup>. However, some studies have found no <sup>8</sup> significant difference in striatum volume between patients with PD and normal controls<sup>[18-21]</sup>. Studies that performed further surface morphometric analyses under automated shape analyses showed: (1) A regional contraction of the posterolateral and ventromedial putamen bilaterally in patients with PD<sup>[14]</sup>; <sup>5</sup> (2) areas of local atrophy in the lateral and <sup>5</sup> medial posterior parts of the bilateral putamen; (3) atrophy locally on the



medial surface of the left caudate nucleus<sup>[21]</sup>; and (4) a reduction in the volume and an inward displacement of the surface of the caudal motor striatum<sup>[22]</sup>. Studies using other machine learning methods have also found local atrophy in the caudate and putamen nuclei, including the caudal portion of the putamen or the middle-posterior putamen and the head of the caudate<sup>[13,23]</sup>. A study attempted <sup>1</sup> to distinguish different stages of PD based solely on the <sup>1</sup> shape analysis of the bilateral caudate nucleus and putamen through an automated process, with balanced accuracies in the range of 59%-85%<sup>[24]</sup>.

Dysfunction of the basal ganglia plays a key role in developing motor and non-motor symptoms in PD<sup>[25]</sup>. When exploring the relationship between volume and symptoms, several studies have shown that greater atrophy of the caudate and putamen in PD is usually associated with more severe motor symptoms and cognitive impairment<sup>[11,17,26,27,59]</sup>. Additionally, some correlation analyses <sup>8</sup> did not find a significant correlation between striatal volume and cognitive or motor symptoms<sup>[10]</sup>.

Local morphological analyses provided more details; <sup>5</sup> local atrophy in the left putamen and thalamus correlated with the right <sup>13</sup> Unified Parkinson Disease Rating Scale (UPDRS) motor scale score, which is the most widely <sup>6</sup> used scale for the clinical studies of PD<sup>[21,28]</sup>. A previous study identified PD with mild cognitive impairment (PD-MCI) with limited atrophy of the right putamen<sup>[29]</sup>. When PD-MCI converted to dementia, <sup>6</sup> smaller local shape volumes were found in the right caudate nucleus of the patients compared to that of patients with PD-MCI who did not convert<sup>[30]</sup>. In addition, <sup>6</sup> logistic regression analysis indicated that the local shape volumes in the right caudate nucleus were significant independent predictors of conversion to dementia in patients with PD-MCI. Distinct structural <sup>1</sup> changes in the caudate and/or putamen are associated with performance in the attention or working



memory domain, fatigue, the severity of rapid eye movement (REM) sleep behavior disorder (RBD), and excessive daytime sleepiness<sup>[26,31-34]</sup>.

Specifically, volume atrophy of the left caudate nucleus or right putamen was found to be more pronounced in the patient cohort<sup>[11,23]</sup>, which may be due to disease lateralization. Previous studies have shown that the decrease in dopamine capacity in the striatum is more pronounced in the contralateral hemisphere on the side with more severe clinical symptoms of PD<sup>[35]</sup>. It has been suggested that the onset of motor symptoms may always occur in one limb, and morphological analysis has revealed a greater degree of striatal atrophy on the contralateral side of the limb where motor symptoms occur<sup>[16]</sup>. Local deformation of the posterior side of the putamen has been reported in several articles. According to the literature, the posterior putamen is directly related to the sensorimotor cortex and is preferentially affected; dopamine depletion is mainly located in this region of the basal ganglia<sup>[10,23,36,37]</sup>. Therefore, we can also infer that the morphological changes in PD can be detected using MRI. Furthermore, we may be able to assess the severity of some symptoms, such as cognitive function in patients with PD, and provide timely interventions for clinical treatment.

### <sup>3</sup> *Shape analysis of the thalamus*

The thalamus is composed of several nuclei that regulate various motor and sensory functions and is usually divided into seven nuclei: the anterior, lateral, ventral, intralaminar, medial, and posterior nuclear groups and the reticular nucleus. Among the nuclei of the thalamus, the ventral thalamus, also known as the subthalamic nucleus (STN), plays an important role in extrinsic inputs reaching the basal ganglia circuitry<sup>[38]</sup>. A study calculated the morphological changes in the STN and found statistically significant differences in the shape of bilateral STN between the PD and control groups,

with the largest deformation site located in the dorsolateral parts of bilateral STNs<sup>[39]</sup>. Patriat *et al*<sup>[65]</sup> showed that the volume of STN was smaller in PD patients compared to healthy controls, which was further validated in the field of 7T MRI. Although thalamic degeneration may represent a site of dopaminergic degeneration in PD, the thalamus is also influenced by hyperactivity in glutamatergic signaling, which may be caused by the loss of dopaminergic neurons in the substantia nigra and striatum<sup>[40]</sup>. Thus, various morphological changes occur in the thalamus of patients with PD. Furthermore, several studies on structural and functional imaging have identified morphological or functional changes in the thalamus in patients with PD. Using manual segmentation, scholars found no significant difference in the thalamus volume between patients with PD and healthy controls<sup>[41]</sup>. They used spherical harmonic-based representation methods and detected significant differences in shape<sup>[41]</sup>. A previous study subdivided the left and right thalamus into 25 subnuclei using automatic methods. It was detected that 21 of the left and 20 of the right thalamic subnuclei had increased volume, accompanied by atrophy in two left subnuclei<sup>[42]</sup>.

More studies have been conducted to correlate thalamic shape changes with clinical symptoms. Nemmi *et al*<sup>[21]</sup> found a significant correlation between local atrophy of the right thalamus and the UPDRS using FSL scripts. However, one study found that surface morphological changes in the thalamus were not associated with disease severity in UPDRS using FreeSurfer segmentation with LDDMM alignment<sup>[20]</sup>. This may be due to differences in segmentation methods and cohort sizes, and the influence of glutamatergic neurons on thalamic morphology requires further investigation.

Moreover, most studies have concluded that altered thalamic morphology is associated with non-motor symptoms. Several studies have found a

relationship between reduced thalamic volume and poor cognitive function in patients with PD<sup>[17,26,27,43,59]</sup>. A more detailed correlation analysis showed that the local shape volume of the bilateral thalamus was a significant independent predictor of the conversion of MCI to dementia. However, the local shape volume of the thalamus<sup>6</sup> was associated with semantic fluency and attentional composite scores<sup>[30]</sup>. In addition, some scholars have found that the severity of other non-motor symptoms in patients with PD<sup>4</sup> is associated with more pronounced thalamic atrophy. Furthermore, they found that such non-motor symptoms include sleep, fatigue, gastrointestinal dysfunction, and REM-RBD<sup>[32,44]</sup>.

The thalamus, one of the output nuclei of the basal ganglia, is markedly affected by dopaminergic and glutamatergic neuronal degeneration. For living subjects, imaging is potentially one of the most practical tools to detect changes in the thalamus. Precise shape analysis shows that the thalamus in PD undergoes major or minor changes. Compared to manual measurements, accurate automated measurements reflect more pronounced variation and more detailed results. Because of the varying progression of neuronal degeneration, thalamus shape analysis in patients with PD presents differently. Hence, future studies using the same methods and similar cohort sizes may show better consistency. Moreover, several studies have demonstrated the relevance of shape alterations and symptoms, especially non-motor symptoms, probably because the thalamic subnuclei play an important role in the transmission of dopaminergic neuronal pathways. However, the sequence in which the onset of symptoms and the changes within the thalamus occur is still unclear. In addition, abnormal STN activity may be associated with motor dysfunction in PD; however, further studies<sup>5</sup> are needed to confirm the relationship between STN shape changes and motor symptoms.

### *Shape analysis of the hippocampus*

As a subcortical structure, the hippocampus is an important brain region that carries the body's cognitive functions and is closely related to learning ability, memory, and emotion regulation. Cognitive impairment is frequently seen in PD; thus, the hippocampus may be an imaging marker of cognitive impairment<sup>[45]</sup>. Scholars have found a reduction in hippocampal gray matter density or thickness through automatic methods in the elderly or patients with cognitive impairment, especially in the CA1, which is one of the four hippocampal subfields called the cornu ammonis<sup>[46-50]</sup>. Several studies on hippocampal morphology have been conducted in patients with PD and normal controls. Using automatic shape analysis, some studies have shown smaller hippocampal volumes in patients with PD than in controls<sup>[16,17,52,54,57]</sup>. There were also reduced local volumes of the hippocampus in patients with cognitive impairment compared with those without cognitive impairment, including the subfields CA1-4<sup>[29,30,51,53,57-59,61]</sup>. Studies have shown that the development of REM-RBD and depression may be associated with a smaller hippocampal volume<sup>[32,55,56]</sup>. This suggests a close relationship between hippocampal atrophy and cognitive function, in which the CA1 may be one of the most notable subfields.

The hippocampus is the main source of cholinergic input to the cerebral cortex, and most studies have shown that the hippocampal volume shrinks in patients with PD. Hippocampal shape analysis has focused on non-motor symptoms in PD, primarily the cognitive function, which matches the function of the hippocampus. The relationship between hippocampal atrophy and cognitive decline has been confirmed in patients with PD in the majority of studies. However, recent studies mostly showed volume results; thus, the surface morphological analysis may be able to link hippocampal subregions

to specific symptoms of cognitive impairment further. The relationship between morphological changes and other symptoms, such as REM-RBD and depression, warrants further investigation.

Furthermore, a large number of studies are also using these automated pipelines to analyze cortical structures in PD. Cerebral cortices are key to human activity and may be altered as a result of unusual activity in PD, such as thinning. Most studies have found atrophy in various parts of the cortex in patients with cognitive impairment. In a longitudinal study, Garcia-Diaz *et al*<sup>[62]</sup> confirmed the thinning of cortical thickness in PD patients with cognitive impairment *vs* those without. Among some symptoms related to the cerebral cortex, Vignando *et al*<sup>[66]</sup> reported a general reduction in occipital, parietal, temporal, frontal, and limbic cortical thickness in patients experiencing hallucinations. Changes in visuospatial and visual supraprereceptual impairment also correlated with cortical thinning in occipital, parietal, and temporal regions in the study by Garcia-Diaz *et al*<sup>[62]</sup>. As for motor symptoms, through the calculation of surface area in a study of PD gait disorders, Wei *et al* found that the larger the surface areas of the left lateral temporal cortex and right inferior parietal cortex, the worse the gait performance<sup>[67]</sup>.

This review focuses on the results of patients on 3T instruments, and participants were scanned using a 1.5T MRI instrument and used manual planar measurements, revealing that the normalized STN and red nuclei volumes were larger in patients with PD than in controls<sup>[60]</sup>. Similarly, 7TMRI imaging revealed atrophy of the overall prefrontal cortex and hippocampus, as well as a reduction in STN volume, for patients with PD<sup>[64,65]</sup>. Although current studies on 7TMRI have focused only on volumetric rather than morphological changes, higher resolution instruments can help us to detect finer structural changes and conduct more structural studies.

## **CONCLUSION**

Methods for the shape analysis of subcortical structures based on MRI data are becoming increasingly diverse and refined, allowing even minor changes to be detected. This study has reviewed previous research on the application of these techniques in PD. In contrast to manual measurements, most studies employ computational methods to maintain objectivity. Volume atrophy can be found in most structures, including the subcortical and cortical areas. Surface-based morphometry detects structural changes that can be associated with clinical symptoms. We found that pathophysiological changes in PD are closely associated with changes in the subcortical structures and that different sub-structural alterations are consistent with specific clinical phenotypes. Therefore, the shape analysis of the subcortical structures can be used as an imaging biological indicator of PD, helping to explain associated clinical symptoms.

**Table 1 Morphological studies in Parkinson's disease**

<b>Subcortical structures</b>	<b>Author</b>	<b>Segmentation methods</b>	<b>Analysis type</b>	<b>Results</b>
Striatum	Geng2006, Walton2018	Manual	Volume	Reduced volume of putamen nuclei
	Pitcher2012, Owens-	Semi-Automatic	Volume	Reduced volume of putamen nuclei
	Sterling2013		Volume	Reduced volume of putamen nuclei
	Geevarghese2015, Vasconcellos2018, Tanner2017, Melzer2012	Automatic	Volume	Reduced volume of putamen nuclei
	Oltra2022	Automatic	Volume	Reduced volume of putamen nuclei (RBD)
	Lee2014, Garg2015	Automatic	Volume	Reduced volume of putamen nuclei
	Garg2015	Automatic	Volume	Reduced volume of putamen nuclei

Thalamus	Kamps2019	Automatic	Volume	Reduced volume (RBD severity)
	Kluger2019	Automatic	Volume	Reduced volume
	Messina2011, Menke2014, Nemmi2015, Khan2019, Gong2019	Automatic	Volume	No significant change
	Chung2017	Automatic	Volume	Locally reduction
	Devignes2021	Automatic	Shape	Locally reduction (cognition)
	Garg2015	Automatic	Shape	Locally reduction
	Gong2019	Automatic	Shape	Locally reduction putamen nuclei
	Tanner2017	Automatic	Shape	Locally reduction caudate nuclei
	Sterling2013	Semi-Automatic	Shape	Locally reduction caudate nuclei
	Nemmi2015	Automatic	Shape	Locally reduction caudate nuclei (
	Tanner2017	Automatic	Shape	Locally reduction putamen nuclei
	Sterling2013	Semi-Automatic	Shape	Locally reduction putamen nuclei
	Sigirli2021	Automatic	Shape	Locally reduction putamen nuclei
	Lee2014	Automatic	Shape	Locally reduction ventromedial p
	Nemmi2015	Automatic	Shape	Locally reduction posterior putan
	Khan2019	Automatic	Shape	Locally reduction motor sub-regio
	McKeown2008	Manual	Volume	no significant d



Hippocampus	Garg2015	Automatic	Volume	Significant difference
	Vasconcellos2018, Mak2014, Sivaranjini2021, Foo2017	Automatic	Volume	Reduced volume
	Niccolini2019	Automatic	Volume	Reduced volume motor symptom
	Kamps2019	Automatic	Volume	Reduced volume
	Chen2020	Automatic	Volume	Increased volume
	Chen2020	Automatic	Volume	Increased volume subnuclei
	Kaya2019	Manual	Shape	Locally reduction STN
	Devignes2021	Automatic	Shape	Locally reduction (cognition)
	Chung2017	Automatic	Shape	Locally reduction (cognition)
	McKeown2008	Automatic	Shape	Locally reduction thalamus
	Garg2015	Automatic	Shape	Net-inward area thalamus
	Wang2018	Automatic	Volume	Reduced volume
	Chen2016	Automatic	density	Reduced density
	Gee2017	Automatic	Volume	Reduced volume (cognition)
	Lee2014, Tanner2018, Radziunas2018, Melzer2012	Automatic	Volume	Reduced volume
	Vasconcellos2018	Automatic	Volume	Reduced volume disease duration
	Yildiz2015, Xu2020	Automatic	Volume	Reduced volume (cognition)

Van2015	Automatic	Volume	Reduced volume (depression)
Rahayel2019	Automatic	Volume	Reduced volume (REM-RBD)
Wilson2019	Automatic	Volume	Reduced volume (cognition, motor)
Luo2021	Automatic	Volume	Reduced volume
Uribe2018	Automatic	Volume	Reduced volume
Becker2021	Automatic	Volume	Reduced volume
Xu2020	Automatic	Volume	Reduced volume (and right GC-DG)
Park2019	Automatic	Volume	Volume asymmetry (CA2-3)
Tanner2017	Automatic	Shape	Locally reduction
Devignes2021	Automatic	Shape	Locally reduction (cognition)

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REM: Rapid eye movement; RBD: Sleep behavior disorder; STN: Subthalamic nucleus; CA: Cornu ammonis (subfields of hippocampus); ML: Molecular layer subfields; GC-DG: Granule cell layer of the dentate gyrus.

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