Cortical thickness and Subcortical volume changes differ between Parkinson disease subtypes

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Research Article

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Abstract

BACKGROUND: To explore the different patterns of cortical thickness and subcortical volume changes between Parkinson disease (PD) subtypes by structural magnetic resonance imaging (MRI).

METHODS: We enrolled 48 clinically confirmed PD patients, including 23 tremor dominant (TD) and 25 postural instability gait dominant (PIGD) subtypes, and 32 matched healthy control (HC) volunteers were also collected, all subjects underwent 3.0 Tesla high-resolution structural MRI scanning. Cortical thickness and subcortical volumetric analysis were estimated using an automated Computational Anatomy Toolbox (CAT12) toolbox.

Results: Compared with the HC group, PIGD patients had significantly thinning cortical thickness in multiple brain regions, such as bilateral inferiorparietal, paracentral, precuneus, superiorfrontal, caudalmiddlefrontal, posteriocingulate, parahippocampal, lateraloccipital and right superiortemporal, supramarginal and parsorbitals. TD patients had slightly thinning focal cortical thickness in bilateral posteriocingulate, left inferioparietal and right precuneus. PIGD patients had thinner cortical thickness in left caudalmiddlefrontal, parahippocampal and right isthmuscingulate and lateraloccipital than TD patients. In addition, subcortical volume atrophy was identified in the bilateral hippocampus and bilateral amygdala of the patients with PIGD, only right hippocampus changes were found in the TD group. Moreover, the largest area under the ROC curve of hippocampus and atrophy ratio, cortical thickness in region of interest (ROI) and combination of hippocampus ratio, atrophy ratio and cortical thickness in ROIs which for distinguish PIGD from TD were 0.733, 0.912 and 0.999 respectively.

Conclusions: Morphometric abnormalities were greater in the PIGD than that in the TD subtype, the disparate patterns of cortical and subcortical degeneration had a potential possibility to distinguish the PD subtypes by MRI perspective in clinical practice.

Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease diagnosed on the basis of motor symptoms, it usually can be divided into tremor dominant (TD) and postural instability gait dominant (PIGD) subtypes. Precious studies have documented that these 2 subtypes differ in their motor and non-motor symptoms [1, 2]. Apart from the marked changes in gait, PIGD patients tend to be poor responsive to deep brain stimulation and levodopa [3], and also have a higher risk of cognitive dysfunction [4, 5], and the default mode network (DMN) integrity is different between PIGD and TD subtypes [6]. Until now, no distinct pathological or imaging findings can distinguish between TD and PIGD subtypes.

Structural MRI of the brain allows for noninvasive assessment of cortical and subcortical morphology [7], and cortical thickness is one of the most sensitive biomarkers used to assess different cerebral conditions [8], Storsve et al also suggested that morphology changes were primarily explained by changes in thickness rather than area [9]. Numerous imaging studies demonstrated that cortical thickness changes occur at relatively early stages of the PD, thinner cortical thickness had been found in
frontal [10], parietal [11], temporal [12], occipital, posterior cingulate [13], fusiform and insula [14] of PD patients when compared with healthy controls. Subcortically, significant volume loss has been shown in bilateral putamen and amygdala [15], hippocampus [16] and thalamus [17,18] in PD patients with poorer cognition, and the different texture and shape of amygdala were found in PD patients with anxiety [19]. So the pathology of Parkinson's disease (PD) is not confined to the nigrostriatal dopaminergic pathway, but also involves widespread cerebral cortical and subcortical areas.

Although, numerous MR studies have been carried out by using quantitative estimation of morphological brain changes associated with PD, little attention has been paid to whether structure MRI improves PD diagnosis or helps differentiating between phenotypes, In recent years, few studies have reported that gray matter atrophy [20] and subcortical atrophy [21], especially hippocampal subfield atrophy [22] of PIGD was greater than that of TD subtype, and reduced frontal thickness was evident in patients with PIGD, profile of motor signs maybe related to unique patterns of cortical atrophy [23]. Conversely, other study has found no significant differences in subcortical volumes between PD motor subtypes [24]. PD subtypes-related pattern of cortical and subcortical damage remains controversial. In addition, up to now, the diagnosis and differential diagnosis of PD subtype mainly depend on subjective judgment [25]. So, an effective and objective method to distinguish TD and PIGD subtype has become an urgent problem.

In the present study, voxel-based MRI method (CAT12) was applied to evaluate cortical thickness and subcortical volume change patterns between the PD subtypes. We speculated that more extensive and more serious cortical thickness abnormalities and subcortical GM atrophy would be in the patients with PIGD group than that in the TD group, the patterns of cortical thickness and subcortical volumes may further help distinguish between PD motor subtypes.

**Methods**

**Study participants**

Forty-eight patients with idiopathic PD (21 male; mean age ± S.D.: 62.5 ± 10.6 years) and 32 age and gender matched healthy controls (HCs; 12 male; mean age ± S.D.: 60.5 ± 7.3 years) were recruited from the Affiliated Hospital of Guizhou Medical University (AHGMU) during 2017 to 2021. The diagnosis of PD was based on the United Kingdom Parkinson's Disease Society Brain Bank criteria, and the patients were followed up to confirm the diagnosis, mostl of patients were at the early stage of PD progression, according to Hoehn Yahr Rating (H&Y) (table 1). All subjects did not report any other neurological or psychiatric diseases, and from FLAIR scans, neither white matter degeneration nor lacunae infarction was found in any subject. All patients had been provided written informed consent and approved by the Ethics Committee of the AHGMU.

**Clinical assessments**

All participants were evaluated with the revised Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in the “on” and practical “off” state (dopaminergic medications held for ≥ 12
hours). Mini-Mental State Examination (MMSE) was acquired for all subjects. Subtype assignments were based on previously established methods [26]. Disease subtype was classified as PIGD when the ratio of total TD rscore/total PIGD score was equal to or less than 1.0, whereas patients with a ratio of 1.5 or more were defined to have TD subtype. When the TD/PIGD ratio was more than 1.0 and less than 1.5, patients were classified to be in the indeterminate class. In this study, 23 patients were classified as TD and 25 as PIGD, 7 cases were indeterminate (exclude from this study, due to the small sample size).

**MRI acquisition**

MRI was performed on a 3.0 Tesla system (Philips Medical Systems, Achieva, Netherlands), using an 8-channel, head-neck-type coil. To avoid artifacts caused by head movement, all subjects were required to remain still and calm. The followings were the MRI parameters of the three-dimensional gradient-echo T1-weighted sequence: repetition time (TR) = 12 ms; echo time (TE) = 6ms; field of view (FOV) 220x220x155mm; voxel size = 0.57x0.57x0.6mm³; matrix size = 384x384, NSA = 1.

**Image processing and analysis**

Voxel-based morphometry (VBM), surface-based morphometry (SBM), as well as region-based morphometry (RBM) were performed by running the default processing pipelines the Computational Anatomy Toolbox 12 software (CAT: http://www.neuro.uni-jena.de/cat/) within SPM12 (SPM: http://www.flion.ucl.ac.uk/spm/) using MATLAB (8.3).

Four steps were performed for cortical thickness analysis. Firstly, cortical thickness and central surface estimation, tissue uses segmentation to estimate white matter distance, and local maxima were projected to other gray matter voxels by using a neighbor relationship described by the WM distance, which is equal to the cortical thickness. Secondly, topology correction, the partial volume correction, sulcal blurring and sulcal asymmetries without sulcus reconstruction were also included in this projection-based thickness. Spherical harmonics were used to repair topological defects. Thirdly, spherical mapping, for inter-participant analysis, a fast algorithm to reduce area distortion was included. Fourthly, spherical registration, volume-based diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration. For inter-subject comparisons, due to the central cortical surfaces were created for both hemispheres separately. The thickness of the left/right hemisphere that was resampled and smoothed with FWHM of 15mm, \( p < 0.005 \) (uncorrected) was considered to be statistically significant.

For VBM analysis, images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), smooth these normalized images by using a 8 mm full width half-height Gaussian smooth kernel. The obtained final voxel size was of 1.5 mm³. At the second statistical level, a two-sample t test was applied to compare smoothed GM images between PD patients and controls, and an absolute threshold mask of 0.1 was used, \( p < 0.005 \) (uncorrected) was set to be statistically significant.

CAT12 was considered as estimation of tissue volumes and surface parameters, after the automatic running procedures, we obtained: 1) the values of regional cortical thickness from 34 regions of interest
(ROIs) in each hemisphere that were defined according to Desikan-Killiany atlas; 2) the values of total intracranial volume (TIV) and subcortical volume from six ROIs in each hemisphere defined according to Neuromorphometrics atlas putamen (Put), caudate nucleus (CauNuc), globus pallidus (Pal), hippocampus (Hip), amygdala (Amy), thalamus (Tha) and nucleus accumbens (AccNuc). For ROI analysis, the comparisons were performed in a ROI-wise manner. ROI analysis was applied to detect gray matter volume and surface parameters alterations in cortical and subcortical deep matter areas. To avoid the influence of varied individual head size on brain tissue volume, the subcortical volumes of each subject were normalized to the individual TIV value and presented as a ratio amplified with a factor of 1,000.

**Statistical analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 27, IBM Corp). The continuous and dichotomous demographic variables using independent t-tests and chi-square tests, respectively. For each structure, left, Right volumes/volumes ratio and cortical thickness were analyzed using analysis of covariance (ANCOVA), after adjusting for age and TIV. Test of Homogeneity of variances was performed, if $p > 0.05$, we use bonferroni to correct; and $p < 0.05$, Dunnett T3 was utilized. Furthermore, we also performed the receiver operating characteristic (ROC) test to assess the ability of cortical thickness and volume ratio of the abnormal MRI morphological changes for distinguishing PD subtypes, and 95% confidence interval (CI) was calculated. All measurement data were presented as mean value and standard deviation. $p < 0.05$ was set to be statistically significant.

**Results**

**Participant characteristics**

The final samples for the current study included 32 HCs, 25 PD patients with PIGD, and 23 PD patients with TD. Table 1 summarizes the descriptive statistics for the demographic and clinical characteristics of the participants. There were no significant differences in age, gender, and education among the groups. The PIGD group had the lowest MMSE scores, which indicated more severe cognitive impairment compared with both the HCs and the TD subtype. Significantly statistical difference was not existed between PIGD and TD for disease stage and MDS-UPDRS-III scores.

**Table 1. Demographic data for Control Subjects, PIGD and TD patients.**
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HC</th>
<th>PIGD</th>
<th>TD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.(female/male)</td>
<td>32(20/12)</td>
<td>25(14/11)</td>
<td>23(13/10)</td>
<td>0.856</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>60.5±7.3</td>
<td>61.8±9.8</td>
<td>63.1±11.6</td>
<td>0.578</td>
</tr>
<tr>
<td>Education, y (mean±SD)</td>
<td>NA</td>
<td>10.0±5.6</td>
<td>9.8±5.7</td>
<td>0.901</td>
</tr>
<tr>
<td>H&amp;Y stage</td>
<td>NA</td>
<td>1.9±0.8</td>
<td>1.6±0.8</td>
<td>0.157</td>
</tr>
<tr>
<td>MDS-UPDRS-III</td>
<td>NA</td>
<td>27.2±12.1</td>
<td>20.9±9.3</td>
<td>0.100</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.1±1.2</td>
<td>25.7±4.7</td>
<td>25.4±3.9</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>TIV cm³</td>
<td>1452.48±123.02</td>
<td>1473.11±139.71</td>
<td>1448.71±91.94</td>
<td>0.744</td>
</tr>
</tbody>
</table>

Abbreviations: HC, healthy control; PIGD, parkinson’s disease patient with postural instability gait difficulty; TD, parkinson’s disease patient with tremor dominant; MMSE, Mini-Mental State Examination; MDS-UPDRS-III, Unified PD Rating Scale part III; H&Y, Hoehn & Yahr. The bold values are statistically significant results.

Cortical thickness

Compared with the HC group, PIGD patients had significantly thinning cortical thickness in multiple brain regions, such as bilateral inferiorparietal, paracentral, precuneus, superiorfrontal, caudalmiddlefrontal, posteriocingulate, parahippocampal, lateraloccipital and right superiortemporal, supramarginal and parsorbitals. TD patients had slightly thinning focal cortical thickness in bilateral posteriocingulate, left inferiorparietal and right precuneus. PIGD patients had thinner cortical thickness in left caudalmiddlefrontal, parahippocampal and right isthmscingulate and lateraloccipital than TD patients. (see Fig 1). Detailed data of abnormal cortical thickness are shown in Table 2.

Fig 1. Cortical atrophy patterns. A) Color maps indicate PIGD patients had significant thinning cortical thickness when compared with healthy controls. B) TD patients had significant thinning cortical thickness when compared with healthy controls. C) PIGD patients had significant thinning cortical thickness when compared with TD patients. (p < 0.005 uncorrected) HC, Healthy control participant; PIGD, PD patients with postural instability gait difficulty symptom; TD, PD patients with tremor dominant symptom.

**Table 2. Cortical thickness measurements.**
<table>
<thead>
<tr>
<th>Region</th>
<th>HC mean ± SD (mm)</th>
<th>PIGD mean ± SD (mm)</th>
<th>TD mean ± SD (mm)</th>
<th>$F$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>caudalmiddlefrontal</td>
<td>2.58±0.19</td>
<td>2.43±0.24</td>
<td>2.50±0.25</td>
<td>3.138</td>
<td>0.049</td>
</tr>
<tr>
<td>caudalmiddlefrontal</td>
<td>2.52±0.18</td>
<td>2.37±0.21</td>
<td>2.47±0.23</td>
<td>3.804</td>
<td>0.027</td>
</tr>
<tr>
<td>inferiorparietal</td>
<td>2.45±0.17</td>
<td>2.33±0.19</td>
<td>2.36±0.24</td>
<td>2.797</td>
<td>0.067</td>
</tr>
<tr>
<td>inferiorparietal</td>
<td>2.40±0.15</td>
<td>2.27±0.20</td>
<td>2.34±0.18</td>
<td>3.697</td>
<td>0.029</td>
</tr>
<tr>
<td>lateraloccipital</td>
<td>1.86±0.15</td>
<td>1.81±0.19</td>
<td>1.85±0.15</td>
<td>0.761</td>
<td>0.471</td>
</tr>
<tr>
<td>lateraloccipital</td>
<td>1.88±0.15</td>
<td>1.79±0.19</td>
<td>1.84±0.13</td>
<td>1.972</td>
<td>0.146</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>2.22±0.15</td>
<td>2.08±0.14</td>
<td>2.18±0.18</td>
<td>5.609</td>
<td>0.005</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>2.25±0.17</td>
<td>2.19±0.17</td>
<td>2.19±0.19</td>
<td>0.975</td>
<td>0.382</td>
</tr>
<tr>
<td>paracentral</td>
<td>1.84±0.16</td>
<td>1.71±0.16</td>
<td>1.79±0.19</td>
<td>4.071</td>
<td>0.021</td>
</tr>
<tr>
<td>paracentral</td>
<td>1.89±0.19</td>
<td>1.76±0.18</td>
<td>1.85±0.16</td>
<td>3.598</td>
<td>0.032</td>
</tr>
<tr>
<td>parsorbitalis</td>
<td>2.51±0.26</td>
<td>2.47±0.24</td>
<td>2.56±0.22</td>
<td>0.711</td>
<td>0.494</td>
</tr>
<tr>
<td>parsorbitalis</td>
<td>2.54±0.25</td>
<td>2.34±0.30</td>
<td>2.48±0.25</td>
<td>4.077</td>
<td>0.021</td>
</tr>
<tr>
<td>posteriorcingulate</td>
<td>2.06±0.16</td>
<td>1.92±0.18</td>
<td>1.94±0.23</td>
<td>4.645</td>
<td>0.012</td>
</tr>
<tr>
<td>posteriorcingulate</td>
<td>2.02±0.15</td>
<td>1.92±0.19</td>
<td>1.93±0.17</td>
<td>3.421</td>
<td>0.038</td>
</tr>
<tr>
<td>precuneus</td>
<td>2.30±0.13</td>
<td>2.17±0.17</td>
<td>2.24±0.15</td>
<td>4.779</td>
<td>0.011</td>
</tr>
<tr>
<td>precuneus</td>
<td>2.28±0.19</td>
<td>2.16±0.19</td>
<td>2.22±0.17</td>
<td>3.114</td>
<td>0.050</td>
</tr>
<tr>
<td>superiorfrontal</td>
<td>2.67±0.17</td>
<td>2.54±0.21</td>
<td>2.60±0.26</td>
<td>2.827</td>
<td>0.065</td>
</tr>
<tr>
<td>superiorfrontal</td>
<td>2.69±0.19</td>
<td>2.56±0.22</td>
<td>2.59±0.24</td>
<td>2.677</td>
<td>0.075</td>
</tr>
<tr>
<td>superiortemporal</td>
<td>2.62±0.18</td>
<td>2.58±0.18</td>
<td>2.58±0.19</td>
<td>0.446</td>
<td>0.642</td>
</tr>
<tr>
<td>superiortemporal</td>
<td>2.68±0.20</td>
<td>2.61±0.16</td>
<td>2.61±0.21</td>
<td>1.307</td>
<td>0.277</td>
</tr>
<tr>
<td>supramarginal</td>
<td>2.54±0.18</td>
<td>2.43±0.17</td>
<td>2.47±0.19</td>
<td>2.992</td>
<td>0.056</td>
</tr>
<tr>
<td>supramarginal</td>
<td>2.47±0.14</td>
<td>2.34±0.21</td>
<td>2.39±0.18</td>
<td>4.028</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Abbreviations: $l$, left; $r$, right. The bold values are statistically significant results. Bonferroni corrected, $p < 0.05$ was set to be statistically significant. The bold values are statistically significant results.

$^a$ Significant difference between HC and PIGD.
Significant difference between HC and TD.

**Subcortical volumes**

Subcortical volume atrophy was identified in the bilateral hippocampus and bilateral amygdala of the patients with PIGD; However, a little right hippocampus changes were found in the TD group (see fig 2). The volumetric results are displayed in Table 3. While mean subcortical volumes were smaller in the PIGD subtype in comparison to the TD subtype for all structures.

![Fig 2](image)

Subcortical atrophy patterns. Color maps indicate A) PIGD patients had significant subcortical atrophy when compared with healthy controls. B) TD patients had significant subcortical atrophy when compared with healthy controls. C) PIGD patients had no significant subcortical atrophy when compared with TD patients. ($p < 0.005$ uncorrected). HC, Healthy control participant; PIGD, PD patients with postural instability gait difficulty symptom; TD, PD patients with tremor dominant symptom.

Table 3. Subcortical volume ratio measurements[$10^{-3}\%$].

<table>
<thead>
<tr>
<th>Region</th>
<th>HC mean ± SD</th>
<th>PIGD mean ± SD</th>
<th>TD mean ± SD</th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lHip</td>
<td>1.22±0.13</td>
<td>1.14±0.17</td>
<td>1.13±0.21</td>
<td>2.637</td>
<td>0.078</td>
</tr>
<tr>
<td>rHip</td>
<td>1.33±0.15</td>
<td>1.25±0.17a</td>
<td>1.20±0.21b</td>
<td>3.901</td>
<td>0.024</td>
</tr>
<tr>
<td>lAmy</td>
<td>0.80±0.12</td>
<td>0.72±0.11a</td>
<td>0.76±0.14</td>
<td>3.392</td>
<td>0.039</td>
</tr>
<tr>
<td>rAmy</td>
<td>0.86±0.12</td>
<td>0.76±0.12a</td>
<td>0.79±0.15</td>
<td>4.683</td>
<td>0.012</td>
</tr>
<tr>
<td>lCauNuc</td>
<td>2.12±0.28</td>
<td>2.17±0.38</td>
<td>2.11±0.32</td>
<td>0.256</td>
<td>0.774</td>
</tr>
<tr>
<td>rCauNuc</td>
<td>2.21±0.29</td>
<td>2.27±0.38</td>
<td>2.20±0.29</td>
<td>0.302</td>
<td>0.741</td>
</tr>
<tr>
<td>lPut</td>
<td>2.60±0.37</td>
<td>2.69±0.42</td>
<td>2.58±0.36</td>
<td>1.142</td>
<td>0.324</td>
</tr>
<tr>
<td>rPut</td>
<td>2.58±0.33</td>
<td>2.62±0.40</td>
<td>2.58±0.35</td>
<td>0.505</td>
<td>0.606</td>
</tr>
<tr>
<td>lAccNuc</td>
<td>0.17±0.02</td>
<td>0.16±0.03</td>
<td>0.17±0.03</td>
<td>0.620</td>
<td>0.540</td>
</tr>
<tr>
<td>rAccNuc</td>
<td>0.17±0.03</td>
<td>0.16±0.04</td>
<td>0.16±0.03</td>
<td>0.139</td>
<td>0.870</td>
</tr>
<tr>
<td>lTha</td>
<td>2.75±0.37</td>
<td>2.69±0.33</td>
<td>2.64±0.52</td>
<td>0.550</td>
<td>0.579</td>
</tr>
<tr>
<td>rTha</td>
<td>2.55±0.45</td>
<td>2.46±0.39</td>
<td>2.56±0.53</td>
<td>0.340</td>
<td>0.713</td>
</tr>
<tr>
<td>lPal</td>
<td>0.43±0.08</td>
<td>0.44±0.08</td>
<td>0.39±0.07</td>
<td>0.966</td>
<td>0.120</td>
</tr>
<tr>
<td>rPal</td>
<td>0.45±0.08</td>
<td>0.47±0.09</td>
<td>0.43±0.08</td>
<td>1.493</td>
<td>0.353</td>
</tr>
</tbody>
</table>

Abbreviations: Hip, hippocampus; Amy, amygdala; CauNuc, caudate nucleus; Put, putamen; AccNuc, nucleus accumbens; Tha, thalamus; Pal, globus pallidus; l, left; r, right. Bonferroni corrected, $p < 0.05$ was
set to be statistically significant. The bold values are statistically significant results.

a Significant difference between HC and PIGD.

**ROC analysis**

The areas under ROC curves (AUCs) value of 0.695, 0.696 were observed for cortical thickness in left parahippocampal and left precentral l, respectively \( p < 0.05 \). The sensitivity, specificity, accuracy and cutoff value of bilateral volume ratio in hippocampus, amygdala, and cortical thickness in bilateral parahippocampal and precentral were shown in Table 4 and Figure 3A and 3B. Additionally, the largest area under ROC curve (AUC) value of 0.999 was found for combination of cortical adn subcortical features of all ROIs between PD subtypes, which was shown in Table 5 and Figure 3C.

**Table 4. ROC analysis of partial subcortical volume ratio and cortical thickness.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Accuracy</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>l Hip</td>
<td>0.537</td>
<td>1.19</td>
<td>0.522</td>
<td>0.720</td>
<td>0.665</td>
</tr>
<tr>
<td>r Hip</td>
<td>0.444</td>
<td>1.27</td>
<td>0.435</td>
<td>0.640</td>
<td>0.509</td>
</tr>
<tr>
<td>l Amy</td>
<td>0.627</td>
<td>0.667</td>
<td>0.913</td>
<td>0.545</td>
<td>0.132</td>
</tr>
<tr>
<td>r Amy</td>
<td>0.557</td>
<td>0.87</td>
<td>0.348</td>
<td>0.84</td>
<td>0.496</td>
</tr>
<tr>
<td>l Parahippocampal</td>
<td>0.695</td>
<td>2.24</td>
<td>0.435</td>
<td>0.96</td>
<td>0.021</td>
</tr>
<tr>
<td>r Parahippocampal</td>
<td>0.502</td>
<td>2.17</td>
<td>0.652</td>
<td>0.48</td>
<td>0.984</td>
</tr>
<tr>
<td>l Precentral</td>
<td>0.696</td>
<td>1.93</td>
<td>0.739</td>
<td>0.680</td>
<td>0.020</td>
</tr>
<tr>
<td>r Precentral</td>
<td>0.663</td>
<td>1.83</td>
<td>0.696</td>
<td>0.64</td>
<td>0.052</td>
</tr>
</tbody>
</table>

The bold values are statistically significant results.

**Table 5. ROC analysis of combination of subcortical volume ratio and cortical thickness.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Area</th>
<th>Std. Error( ^a )</th>
<th>Asymptotic Sig.( ^b )</th>
<th>Asymptotic 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Volume_all</td>
<td>0.733</td>
<td>0.075</td>
<td>0.006</td>
<td>0.586</td>
</tr>
<tr>
<td>Thickness_all</td>
<td>0.912</td>
<td>0.040</td>
<td>0.000</td>
<td>0.834</td>
</tr>
<tr>
<td>Volume_Thickness_all</td>
<td>0.999</td>
<td>0.002</td>
<td>0.000</td>
<td>0.996</td>
</tr>
</tbody>
</table>

The bold values are statistically significant results.

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

**Discussion**

In this current study, we investigated the cortical thickness and subcortical volumes in TD and PIGD patients and found that 1) PIGD patients had significant thinner cortical thickness in multiple brain regions, including bilateral frontal, parietal, temporal and limbic lobe, TD patients had slightly thinning cortical thickness in left parietal, limbic lobe and in right frontal, temporal. In addition, subcortical volume atrophy was identified in the bilateral hippocampus and amygdala of the patients with PIGD, and a little right hippocampus changes were found in the TD group; 2) the areas under the ROC curves of cortical thickness of left parahippocampal and precentral and combination features of cortical and subcortical atrophy patterns may be helpful in distinguishing PIGD from TD subtype. Our results are consistent with previous work, which similarly found more extensive GM atrophy in several brain areas including motor as well as cognitive, associative, and limbic regions in the PIGD group [20]. So, findings of these study may support the idea that regional morphologic changes is associated with the two different PD motor subtypes.

Compared with HCs, PIGD patients suggested lower cortical thickness in widespread regions of frontal regions (bilateral superior frontal, caudal middle frontal, paracentral, precuneus, and right pars orbitals). TD patients manifested slightly thinner cortical thickness only in right superior frontal. According to previous studies, abnormal structural changes in the frontal lobe maybe presented during the progression of cognitive decline [27, 28]. And also, the inferior frontal gyrus maybe play a crucial role in keeping normal response inhibition and cognitive executive function [29]. In Chung's study [27], more extensive cortical thinning, particularly in the frontal regions were found in PD patients who converted dementia, compared to those who did not convert to dementia. Wolters [12] also found that gray matter abnormalities in frontal are associated only with cognitive decline in early stages of PD. In this present study, we also found both PIGD and TD patients had significantly lower MMSE scores than that in HC subjects, but we couldn't find any association between cortical thickness of frontal areas and MMSE scores, this may be due to the small sample size of this study.

Apart from frontal atrophy, thinner cortical thickness of the parieto-temporal association cortex, including the bilateral inferior parietal, precuneus and right superior temporal were found in PIGD patients. But in TD patients, thinner cortical thickness were found restricted to left inferior parietal and right precuneus. These results are in line with Braak's hypothesis of PD progression: Firstly, The temporal lobe were affected by Lewy bodies, Then the insula, prefrontal, parietal and occipital lobes, Finally, the primary sensory and motor areas were influenced [30]. Some VBM or cortical thickness studies have found that early, untreated PD patients may already have atrophy of gray and white matter in the temporal lobe [31, 32], and PD patients with mild cognitive impairment (MCI) and dementia are mainly associated with marked temporal lobe atrophy [33, 34]. As a consequent, lower cortical thickness in the temporal regions may indicate impaired cognitive function in PD patients.
Lower cortical thickness was also found in parietal (the bilateral inferiorparietal, paracentral, precuneus, right supramarginal) regions, which are mainly involved in the visuospatial and visuoperceptual functions [35]. Visual dysfunction is common in PD, including deficits in visual acuity, contrast sensitivity, color vision, visuospatial construction, motion perception, spatial neglect, and visual hallucinations [36]. Previous studies have found that PD patients with visual hallucinations have superior parietal [37] and cuneus [38] atrophy compared with patients without visual hallucinations. Besides, progressive thinning of the parieto-temporal sensory association cortices related to disease duration also seems to be related in part to the exacerbation of bradykinesia and the axial motor symptoms of PD [39]. Chaudhary et.al [40] found that fronto-parietal and temporal regions suffer cognition associated cortical thinning. These inconsistencies may be related to the different clinical symptoms they focused on.

In addition, as for different cortical thickness changes between PIGD and TD subtypes, this study also explored the changes of subcortical volumes in these PD patients. Subcortical volume atrophy was identified in the bilateral hippocampus and bilateral amygdala of the patients with PIGD, a little bilateral hippocampus changes were found in the TD group. The results were consistent with a recently large-scale collaboration study [15], in this study, the bilateral amygdala were affected first at an early symptomatic stage, with reduced bilateral hippocampal volumes at advanced symptomatic stage. Previous studies also demonstrated that smaller amygdala and hippocampus associated with PD dementia.

Hippocampus is a parts of the limbic system, lower hippocampal volume in PD was always suggested to be predictive of the progression of cognitive impairment [22]. These morphological changes of hippocampus differ in PD subtypes may be in consistent with precious suggestion that PIGD patients have a higher association with cognitive dysfunction [2, 4, 5]. However, we found no difference in cognitive impairment between PD subtypes due to the small sample size in our study. Moreover, In humans, the amygdala is known to be an interface between external stimuli and behavioral as well as cognitive responses to anxiety [41]. Anxiety is frequent in PD patients and has a negative impact on disease symptoms and quality of life [19]. Based on animal studies, the existence of an anatomo-functional network called the “fear circuit” was postulated whose hub is the amygdala [42, 43]. In our study, significant volume loss of the amygdala was observed in the PIGD patients, but not in TD patients, this results maybe suggested that PIGD have a higher risk of anxiety.

Compared with TD subtype, thinner cortical thickness in left caudalmiddlefrontal, parahippocampal and right isthmuscingulate and lateraloccipital were found in PIGD subtype, and analysis from ROC curve also demonstrated that the largest area under the ROC curve of cortical thickness in all these ROIs maybe useful in distinguishing PIGD from TD subtypes. However, no subcortical volume changes were found between PIGD and TD subtypes, these results may suggest that cortical thickness tends to be more sensitive in distinguishing PIGD from TD subtypes.

This study has several limitations that need to be mentioned. Firstly, due to the small sample size, especially the TD cohort (n = 23). It might be prone to Type II error in the findings, which reduced the
statistical power of our findings. This study can indeedly reveal a trend of subcortical atrophy patterns and cortical atrophy patterns between PD subtypes, for subcortical atrophy patterns and cortical atrophy patterns analysis, two statistical analysis were adopted, SBM and ROI analysis for cortical thickness, and VBM and ROI analysis for subcortical atrophy. Secondly, the inclusion of a small number of subjects from single centers, heterogeneity in patient characteristics, including disease duration, disease severity, cognitive status and other non motor-symptom clinical features were not clearly classified, future studies will assess wider samples of PD patients in the different stages of the disease. Thirdly, Morphological changes of PD in brain structure have closely association with clinical symptoms, and determine the progression of the disease. In future research, we will conduct longitudinal observations of changes in patients with PD.

Conclusion

In conclusion, the pathology of Parkinson's disease leads to different cerebral morphological changes in these two subtypes. For cortical thickness, our studies found more severe and extensive thinning of cortical thickness in PIGD patients, but TD patients showed slightly thinning cortical thickness in fewer regions. For subcortical volumes, bilateral hippocampus and amygdala atrophy were detected in PIGD subtype, little right hippocampus changes were found in the TD group. In addition, combination features of cortical and subcortical atrophy patterns maybe quantitatively for assessing the morphological changes between PIGD and TD subtypes. So, our findings may help distinguish between PD motor subtypes, and future longitudinal studies will be designed to investigate morphological changes with more nonmotor symptoms (cognitive impairment, anxiety and depression) between these two PD subtypes.

Declarations

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Author contributions

HMM, YH, LPG and GB contributed to conception and design of the study. GKL and YJH organized the database. HMM and LPG performed the statistical analysis. HMM wrote the first draft of the manuscript. LPG, YH and GB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study is approved by the Ethics Committee of the Affiliated Hospital of GuiZhou Medical University. All patients and their legal guardians provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interests

The authors declare no potential conflict of interest.

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References


**Figures**

![Figure 1](image-url)

**Figure 1**
Cortical atrophy patterns. A) Color maps indicate PIGD patients had significant thinning cortical thickness when compared with healthy controls. B) TD patients had significant thinning cortical thickness when compared with healthy controls. C) PIGD patients had significant thinning cortical thickness when compared with TD patients. \( p < 0.005 \) uncorrected. HC, Healthy control participant; PIGD, PD patients with postural instability gait difficulty symptom; TD, PD patients with tremor dominant symptom.

Figure 2

Subcortical atrophy patterns. Color maps indicate A) PIGD patients had significant subcortical atrophy when compared with healthy controls. B) TD patients had significant subcortical atrophy when compared with healthy controls. C) PIGD patients had no significant subcortical atrophy when compared with TD patients. \( p < 0.005 \) uncorrected. HC, Healthy control participant; PIGD, PD patients with postural instability gait difficulty symptom; TD, PD patients with tremor dominant symptom.

Figure 3

Sensitivity and specificity of subcortical volume ratio in hippocampus, amygdala (A) and cortical thickness in ROIs (B) and combination features of cortical thickness and subcortical atrophy in ROIs (C) between PD subtypes.