Original Article

BDNF rs6265 single-nucleotide polymorphism is involved in levodopa-induced dyskinesia in Parkinson's disease via its regulation of the cortical thickness of the left postcentral gyrus

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Background: Brain-derived neurotrophic factor (*BDNF*) gene rs6265 single-nucleotide polymorphism (SNP) is thought to be involved in neuroplasticity and influence the development of levodopa-induced dyskinesia (LID) in Parkinson's disease (PD). This study aimed to determine how the *BDNF* rs6265 SNP regulates cortical thickness and to investigate the association between *BDNF* and the pathological mechanisms of LID in PD.

Methods: This cross-sectional study recruited 75 patients with PD, including 37 patients with LID and 38 patients without LID, and 33 healthy controls. All the participants underwent T1-weighted magnetic resonance imaging (MRI) scans, clinical evaluations, and *BDNF* rs6265 genotyping. Two-way factorial analysis of covariance (ANCOVA) was used to explore the primary effects of disease status, rs6265 genotype, and their interactions on cortical thickness. Associations between cortical thickness in the regions of the brain affected by disease status-genotype interactions and clinical symptoms were detected using Spearman's rank-order correlation. Receiver operating characteristic (ROC) curve analysis was used to test cortical thickness measurements as an indicator of LID.

Results: The main effects of disease status were observed in the right pars orbitalis (F=4.229, P=0.017), medial orbitofrontal cortex (F=3.639, P=0.030), and left banks superior temporal sulcus (F=3.172, P=0.046). The left pars orbitalis (F=4.541, P=0.036) and lingual gyrus (F=4.307, P=0.041) were thicker in carriers of the CC genotype than in carriers of the TC/TT genotype. Interaction between disease status and genotype showed that in the LID group, carriers of the CC genotype had a thicker left postcentral gyrus (mean difference =0.103, 95% confidence interval, 0.036 to 0.107, Bonferroni-corrected P<0.005) than did carriers of the TC/TT genotype, whereas no difference was found in the non-LID and healthy control (HC) groups. In carriers of the CC genotype, the cortical thickness of the left postcentral gyrus could identify whether patients with PD had LID, with an area under the receiver operating curve (AUC) of 0.757 (P=0.033, optimal cut-off =2.102). The cortical thickness of the left postcentral gyrus was also positively correlated with the Unified Dyskinesia Rating Scale (UDysRS) score in the LID-CC subgroup (r=0.825, P=0.001).

Conclusions: The *BDNF* rs6265 SNP might be associated with dyskinesia symptoms in patients with PD and LID through its regulation of cortical thickness in the left postcentral gyrus.

Keywords: Levodopa-induced dyskinesia (LID); Parkinson's disease (PD); Brain-derived neurotrophic factor rs6265 (*BDNF* rs6265); imaging genetics; cortical thickness

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Introduction

Almost 50% of patients with Parkinson's disease (PD) develop levodopa-induced dyskinesia (LID) after receiving levodopa (L-dopa) treatment for more than 5 years, which greatly limits the efficacy of this medication (1). Several risk factors, including age of onset, disease severity, and daily dose of L-dopa, are associated with the occurrence of LID in patients with PD (2-4), although these factors do not explain the underlying mechanisms of the condition. The pathogenesis of LID is therefore still unclear. Neuroplasticity is considered to play an important role in nervous system compensation and repair after injury through dynamic regulation and adaptation to internal and external environment changes. LID is known to result from abnormal plasticity of dopaminergic neurons in the cortical-basal ganglia motor pathway caused by long-term non-physiological dopaminergic stimulation (1). Abnormal synaptic plasticity in the somatosensory and motor cortex is also believed to contribute to the onset of LID (5).

Brain-derived neurotrophic factor (*BDNF*), located at 11p14.1, has been widely studied, and the secondary T allele of the rs6265 (C196T) locus has been found to be associated with the conversion of valine (Val) to methionine (Met) encoded by codon 66. In addition, the *BDNF* rs6265 single-nucleotide polymorphism (SNP) modulates neuroplasticity by regulating BDNF levels (6,7). Foltynie *et al*. (8) found that the *BDNF* rs6265 genotype was closely related to the onset time of LID in patients with PD; specifically, the LID onset time was later in carriers of the CC genotype than in carriers of the T allele. However, Cheshire *et al*. (9) suggested that the SNP loci of *BDNF* did not affect the prevalence rate or onset time of LID. The role of the *BDNF* rs6265 SNP is clearly still controversial in LID, and the underlying mechanisms of LID require further study.

Structural magnetic resonance imaging (MRI) is a traditional and reliable neuroimaging method. Cortical thickness, gray matter (GM) volume, and other measurements have been widely used to study structural changes in the brains of patients with PD and LID. Cerasa *et al*. found that compared to patients who did not have LID, those with LID presented with higher bilateral inferior frontal gyri GM volumes (10) and a thicker right inferior frontal sulcus (11). One of our previous studies also confirmed significantly increased GM volumes in the precentral gyrus in patients with PD and diphasic dyskinesia (12). In past studies, we have also used imaging genetics to investigate the role of multiple gene polymorphisms in patients with PD by exploring alterations in brain structure and function (13,14). However, few similar studies have been carried out in patients with PD and LID. To our knowledge, the present study is the first to investigate how the *BDNF* rs6265 SNP specifically regulates cortical thickness and explore the relationship between the *BDNF* rs6265 SNP and the pathological processes of LID. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1018/rc).

Methods

Study participants

Participant recruitment for this cross-sectional study began in March 2017 and the expected sample size was reached in November 2019. A total of 83 patients with a diagnosis of idiopathic PD were enrolled from the Department of Neurology at the First Affiliated Hospital of Nanjing Medical University.

The inclusion criteria for the study were as follows: (I) participant met the United Kingdom Parkinson's Disease Society Brain Bank Research criteria; (II) participant had been receiving L-dopa treatment for at least 6 months and their daily L-dopa dose was ≥200 mg; (III) participant had been on a stable drug dose for at least 4 weeks; (IV) participant had no contraindications to MRI scanning; (V) participant showed no evidence of abnormal anatomical brain structure; and (VI) participant had no obvious cognitive impairment [Mini-Mental State Examination

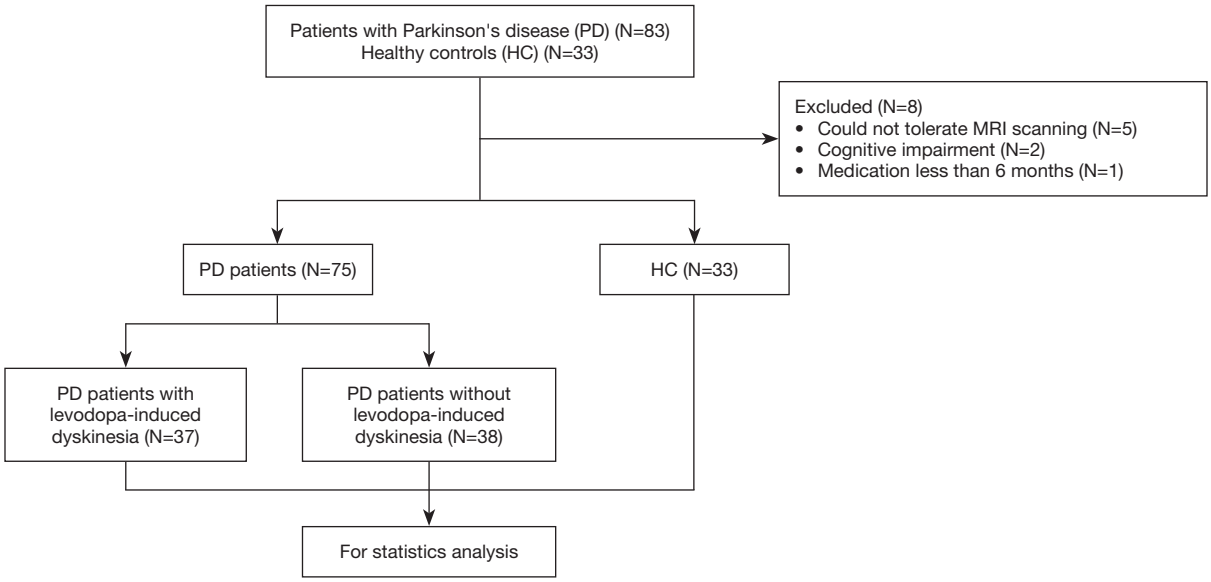

Figure 1 Study flow diagram. PD, Parkinson's disease; HC, healthy control; N, numbers; MRI, magnetic resonance imaging.

(MMSE) score >24].

Two experienced neurologists determined whether each patient with PD had peak-dose LID by assessing the patient's self-described clinical symptoms and observing their involuntary movements at 1 to 2 h after levodopa administration. After screening, 8 patients with PD were excluded (5 could not tolerate MRI scanning, 2 had significant cognitive impairment, and 1 had been receiving medication for less than 6 months). The remaining 75 patients were divided into an LID group (n=37, all of whom were peak-dose LID) and a non-LID group (n=38), depending on whether LID was present or absent. Thirty-three healthy control (HC) participants matched to the participants with PD by age, sex, and education were also enrolled in the study. None of the HC participants had a family history of PD, cognitive impairment, or other neuropsychiatric diseases. A flow diagram of the selection process is shown in *Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2016-SRFA-094). Informed consent was obtained from all the participants.

Clinical evaluations

The demographic and clinical characteristics of all the participants were recorded. For each of the patients with PD, we also calculated the total L-dopa equivalent daily dose (LEDD) (15). To minimize any pharmacological impact, the patients were required to stop using anti-Parkinson's medication at least 12 h before their clinical evaluations. The Unified Parkinson's Disease Rating Scale III (UPDRS-III) (16) and the Hoehn and Yahr (H&Y) (17) staging scale were used to evaluate the severity of participants' motor symptoms, with higher scores indicating more severe symptoms. The Tinetti test was used to assess balance (items 1 to 9) and gait function (items 10 to 16) (18). Also, the Hamilton Anxiety Rating Scale (HAM-A) (19) and Hamilton Depression Rating Scale (HAM-D) (20) were adopted to determine whether patients had symptoms of anxiety or depression. The cognitive status of the patients was quantified according to the MMSE (21) and the Frontal Assessment Battery (FAB) (22). Participants were also evaluated using the Epworth Sleepiness Scale (ESS) (23) and the Fatigue Severity Scale (FSS) (24). The Unified Dyskinesia Rating Scale (UDysRS) (25) was used for assessment when a patient with PD developed dyskinesia. The UDysRS is a comprehensive and reliable rating tool for dyskinesia in PD, and patients with more severe involuntary movement symptoms tend to score higher on this scale. All clinical evaluations were completed by trained neurologists. The criteria for rating the severity of these clinical factors are provided in Appendix 1.

DNA isolation and SNP genotyping

Peripheral venous blood samples were taken from the antecubital vein of participants and stored in a refrigerator at −80 ℃ for the *BDNF* rs6265 SNP genotyping. DNA isolation and SNP genotyping were completed by Beijing Liuhe Huada Genome Technology Co., Ltd. A DNA extraction kit (BioTeKe Corporation, Wuxi, China) was used to extract the genomic DNA from each sample according to the manufacturer's instructions. Primer designs for the SNP sites were evaluated using Assay Designer4.0 software (Agena Bioscience Inc., San Diego, America), and three primers corresponding to SNP sites were synthesized using the polyacrylamide gel electrophoresis primer purification method. Polymerase chain reaction (PCR) was performed following the kit manufacturer's instructions. The products of the PCR were treated with shrimp alkaline phosphatase to remove free triphosphate base deoxynucleotides from the system. Then, a single-base extension (SBE) reaction was carried out to form an SBE product complementary to the SNP genotype to be detected, and the extension product was purified with resin. A MassARRAY Nanodispenser RS1000 sampling instrument was used. The purified extended products were transferred to a SpectroCHIP chip and analyzed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Original data and a genotyping map were obtained using MassARRAY TYPER4.0 software (Agena Bioscience, Inc., San Diego, America). As in previous studies (26,27), participants in the LID, non-LID, and HC groups were further divided into subgroups according to their rs6265 genotype (CC or TC/TT) as follows: LID-CC, n=12; LID-TC/TT, n=25; non-LID-CC, n=12; non-LID-TC/TT, n=26; HC-CC, n=11; HC-TC/TT, n=22 (*BDNF* rs6265 allelic variant C → T).

MRI acquisition

Two experienced radiologists used a 3.0 T Siemens MAGNETOM Verio whole-body MRI system equipped with eight-channel, phased-array head coils (Siemens Medical Systems, Earlngen, Germany) to obtain brain MRI scans from each participant. We provided the participants with earplugs and foam pads to reduce head movement during image acquisition and lessen the impact of the machine noise. T1-weighted structural MRI images were obtained using a three-dimensional magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: repetition time (TR) =1,900 ms, echo time (TE) =2.95 ms, flip angle (FA) =9°, matrix size =256×256, field of view (FOV) =230×230 mm^2, layers =160, slice thickness =1 mm, no slice gap. All images were examined, and those with incomplete brain tissue or artifacts were excluded.

Cortical thickness

Cortical thickness analysis was performed using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/, version 6.0) and high-resolution T1-weighted MRI. Briefly, the steps were as follows (28,29): (I) removal of the skull and other non-brain data, (II) automated Talairach transformation, (III) normalization of gray values, (IV) segmentation of the GM and white matter, and (V) automated topology correction and surface deformation. Each participant was evaluated to ensure image processing accuracy. Cortical thickness was taken to refer to the average distance between the gray-white matter interface and the leptomeningeal surface in the brain region. Finally, the cerebral cortex was divided into 74 brain regions on the left and right (Destrieux map), and the cortical thickness of each brain region was calculated.

Statistical analysis

We used imaging genetics to explore the special regulatory effect of the *BDNF* rs6265 SNP on cerebral cortical thickness in patients with PD and LID. Analyses of demographic information, clinical evaluation data, and MRI data were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation, while categorical variables were described as frequency. The Chi-square test was applied to measure the Hardy-Weinberg Equilibrium (HWE) of *BDNF* rs6265 and sex distribution among subgroups. Normality of the data was detected using the Kolmogorov-Smirnov (K-S) test. Depending on whether the data were normally distributed, one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was selected to compare differences in demographic (age and education) and clinical data between subgroups with different disease status and genotypes. Due to the normality of data distribution, a two-sample *t*-test was used to compare differences in UDysRS scores between the different genotype subgroups within the LID group. A P value <0.05 was considered significant.

A two-way factorial analysis of covariance (ANCOVA:

Table 1 Participant demographic and clinical evaluation data

Variable	PD LID		PD non-LID		HC		P value
	CC	TC/TT	CC	TC/TT	CC	TC/TT	
N	12	25	12	26	11	22	0.988[a]
Sex (M/F)	8/4	10/15	7/5	15/11	8/3	15/7	0.204[a]
Age (years)	57.83±13.74	61.96±7.72	56.83±9.82	62.15±7.13	58.82±6.40	63.14±5.19	0.803[b]
Education (years)	10.25±2.70	9.68±3.68	10.58±3.15	10.23±3.57	11.27±4.71	12.45±3.39	0.106[c]
Disease duration (years)	8.33±3.94	9.52±4.46	5.75±2.09	6.12±3.41	NA	NA	0.002[c]*
LEDD	602.60±236.89	719.68±149.01	586.33±109.25	683.90±294.72	NA	NA	0.086[c]
H&Y stage	2.63±0.64	2.40±0.52	1.75±0.50	2.31±0.69	NA	NA	0.003[c]*
UPDRS-III	33.50±11.26	34.28±12.29	25.08±10.33	35.73±16.34	NA	NA	0.219[c]
MMSE	28.92±0.90	27.76±1.51	28.42±1.24	28.04±1.34	NA	NA	0.078[c]
HAM-A	14.08±7.74	14.72±9.38	9.58±5.14	14.04±7.10	NA	NA	0.180[c]
HAM-D24	12.42±10.26	15.20±11.39	7.75±5.15	13.12±8.39	NA	NA	0.196[c]
FAB	16.30±1.25	15.54±2.50	16.17±2.48	15.00±3.74	NA	NA	0.723[c]
ESS	7.09±5.22	8.00±6.43	7.33±4.60	10.44±10.69	NA	NA	0.942[c]
FSS	37.64±18.00	30.57±12.18	31.33±13.67	32.48±15.86	NA	NA	0.832[b]
Tinetti balance	11.40±4.93	12.71±3.90	15.00±1.13	12.38±4.27	NA	NA	0.168[c]
Tinetti gait	8.00±3.53	7.83±3.70	10.17±1.90	8.92±3.11	NA	NA	0.063[b]
UDysRS	26.25±15.58	28.00±19.06	NA	NA	NA	NA	0.784[d]

Values except sex are expressed as mean ± standard deviation. [a], Chi-square test; [b], One-way analysis of variance (ANOVA); [c], Kruskal-Wallis test; [d], two-sample *t*-test; *, P<0.05 was considered significant. PD LID, Parkinson's disease with levodopa-induced dyskinesia; PD non-LID, Parkinson's disease without levodopa-induced dyskinesia; HC, healthy control; N, number; M, male; F, female; y, years; LEDD, levodopa-equivalent daily dose; H&Y stage, Hoehn and Yahr stage [0–5]; UPDRS-III, Unified Parkinson's Disease Rating Scale III [0–108]; MMSE, Mini-Mental State Examination >24; HAM-A, Hamilton Anxiety Rating Scale [0–56]; HAM-D24, Hamilton Depression Rating Scale [0–78]; FAB, Frontal Assessment Battery [0–18]; ESS, Epworth Sleepiness Scale [0–24]; FSS, Fatigue Severity Scale [9–63]; UDysRS, Unified Dyskinesia Rating Scale [0–104]; NA, not applicable.

disease status × genotype; disease status: LID, non-LID, or HC; genotypes: CC or TC/TT) was used to determine the primary effects of disease status and *BDNF* genotype, and their interactions on the cortical thickness of each brain region, taking age, sex, years of education, disease duration, and H&Y stage as covariates. Additionally, we performed *post hoc* tests to further explore intragroup differences. The statistical threshold was P<0.05 with Bonferroni correction. Spearman's correlation analysis was used to explore correlations between clinical scale scores and the cortical thickness of certain brain regions. To evaluate the accuracy of cortical thickness measurements as indicators of LID in the regions of the brain affected by disease status-genotype interactions, receiver operating characteristic (ROC) curves were drawn and the areas under the curves (AUCs) were calculated. A P value <0.05 was considered significant.

Results

Demographic and clinical data

The frequency of BDNF rs6265 genotypes was consistent with the HWE (LID: χ^2=0.620, P=0.431; non-LID: χ^2=0.012, P=0.914; HC: χ^2=0.142, P=0.707). Differences in demographic and clinical data are shown in *Table 1*. Disease duration (P=0.002) and H&Y stage (P=0.003) differed significantly between the four subgroups of different disease statuses and genotypes in patients with PD. Also, patients in the LID group had a longer disease duration (median difference =3.000, 95% confidence interval, 2.000 to 5.000,

Table 2 The effects of disease status and genotypes on cortical thickness in CC and TC/TT genotypes in all participants

Factor	Brain region	F value	P value
Main effect of disease status	Right pars orbitalis	4.229	0.017
	Right medial orbitofrontal cortex	3.639	0.030
	Left banks superior temporal sulcus	3.172	0.046
Main effect of genotypes	Left pars orbitalis	4.541	0.036
	Left lingual gyrus	4.307	0.041
Disease status × genotype interaction	Left postcentral gyrus	4.451	0.014

Two-way factorial analysis of covariance (ANCOVA: disease status × genotypes, disease status: LID, non-LID and HC, genotypes: CC and TC/TT carriers) was performed, adjusting for age, gender, years of education, disease duration, and H&Y stage. A Bonferroni-corrected threshold was set at P<0.05. LID, levodopa-induced dyskinesia; HC, healthy control; H&Y stage, Hoehn and Yahr stage; ANCOVA, analysis of covariance.

P=0.000) and a more severe H&Y stage (median difference =0.500; 95% confidence interval, 0.000 to 0.500; P=0.013) than those in the non-LID group. Post hoc analysis revealed that, in both the LID group and the non-LID group, there were no significant differences in disease duration or H&Y stage between the CC and TC/TT subgroups. No significant differences were observed in other demographic and clinical data in relation to disease status.

Cortical thickness

The results of two-way ANCOVA of cortical thickness are summarized in *Table 2*. We used age, sex, years of education, disease duration, and H&Y stage as the covariates. The primary effects of disease status (LID, non-LID, or HC) were observed in the right pars orbitalis (F=4.229, P=0.017), the medial orbitofrontal cortex (F=3.639, P=0.030), and the left banks superior temporal sulcus (F=3.172, P=0.046) (*Table 2*, *Figure 2*). However, post hoc analysis revealed that while there was no difference in the right medial orbitofrontal cortex or the left banks superior temporal sulcus between the LID and non-LID groups, patients in the LID group showed greater cortical thickness in the right pars orbitalis than did those in the non-LID group (mean difference =0.103; 95% confidence interval, 0.002 to 0.205; P=0.045). The primary effects of genotype (CC or TC/TT) were noted in the left pars orbitalis (F=4.541, P=0.036) and the lingual gyrus (F=4.307, P=0.041) (*Table 2*, *Figure 2*). These brain regions were thicker in the CC-genotype subgroups than they were in the TC/TT-genotype subgroups. Furthermore, the interaction between disease status and genotype was shown to have a significant effect in the left postcentral gyrus (F=4.451, P=0.014) (*Table 2*, *Figure 2*). Post hoc tests in the LID group showed that carriers of the CC genotype had a thicker left postcentral gyrus (mean difference =0.103; 95% confidence interval, 0.036 to 0.107; Bonferroni correction, P<0.005) than did carriers of the TC/TT genotype, but no such differences were found in the non-LID and HC groups (*Figure 3*).

Correlation analysis

Correlation analysis showed that the cortical thickness of the left postcentral gyrus (r=0.825, P=0.001) was positively associated with UDysRS score in the LID-CC group (*Figure 4*). However, these correlations were not observed in the LID-TC/TT group. Furthermore, no correlation was discovered between the cortical thickness in the region of the brain affected by the disease status-genotype interaction and other scale scores including the UPDRS-III, MMSE, HAM-A, HAM-D, FAB, ESS, FSS, and Tinetti balance and gait scales. Furthermore, there was no correlation between the cortical thickness of the right pars orbitalis and the UDysRS score in the LID group.

ROC curve analysis

ROC curve analysis revealed that in carriers of the CC genotype, the cortical thickness of the left postcentral gyrus was a significant indicator of whether PD was complicated with LID (AUC =0.757, P=0.033) (*Figure 5*). The optimal cut-off was 2.102 mm, which had sensitivity and specificity of 66.7% and 75.0%, respectively. However, a similar effect was not found in carriers of the TC/TT genotype (AUC =0.482, P=0.828) or in patients with PD overall (AUC =0.579, P=0.239).

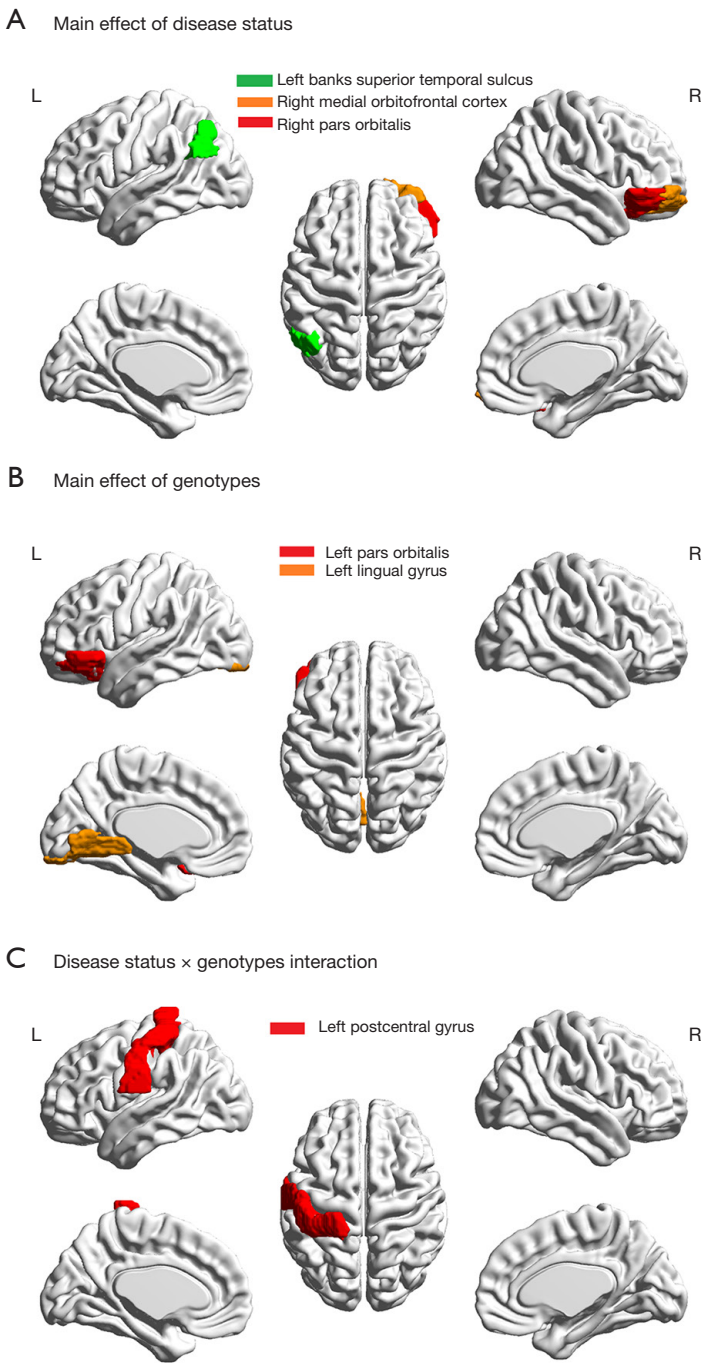

Figure 2 Disease status × genotype ANCOVA of cortical thickness. (A) The main effects of disease status on cortical thickness in the right pars orbitalis, medial orbitofrontal cortex, and left banks superior temporal sulcus of patients with PD with and without LID and in HC participants. (B) The main effects of genotype on cortical thickness in the left pars orbitalis and lingual gyrus of all participants with the CC or TC/TT genotype. (C) The effect of interaction between disease status and genotype in the left postcentral gyrus. Findings were obtained via two-way factorial analysis of covariance. (ANCOVA: disease status × genotypes, disease status: LID, non-LID, and HC, genotypes: CC and TC/TT), adjusting for age, sex, years of education, disease duration, and H&Y stage. A Bonferroni-corrected threshold was set at $P<0.05$. R, right; L, left; PD, Parkinson's disease; LID, levodopa-induced dyskinesia; HC, healthy control; H&Y stage, Hoehn and Yahr stage; ANCOVA, analysis of covariance.

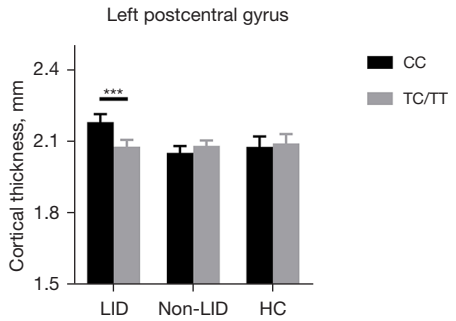

Figure 3 Post hoc tests of the interaction between disease status and genotype. Carriers of the CC genotype show increased cortical thickness in the left postcentral gyrus relative to carriers of the TC/TT genotype in the LID group, whereas there is no such difference in the non-LID and HC groups. Post hoc tests are Bonferroni-corrected with a significant difference: ***, P<0.005. LID, levodopa-induced dyskinesia; HC, healthy control.

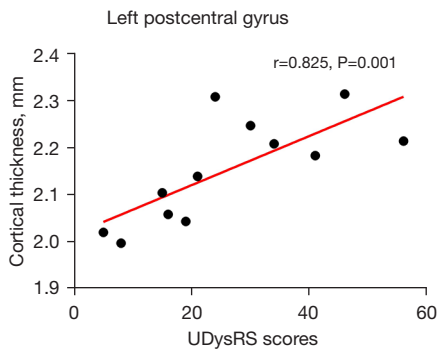

Figure 4 Correlation analysis between UDysRS score and the cortical thickness of the left postcentral gyrus in the LID-CC group. In patients with LID and the CC genotype, the cortical thickness of the left postcentral gyrus is positively associated with UDysRS score (r=0.825, P=0.001). UDysRS, unified dyskinesia rating scale; LID, levodopa-induced dyskinesia.

Discussion

In the present study, we investigated the potential modulative effect of genetic variants of the *BDNF* on cortical thickness in patients with PD and LID using imaging genetics. We found interactions between disease status and genotype affected the left postcentral gyrus, and that the cortical thickness of this region in the LID-CC group was substantially greater than that in the LID-TC/TT group. Furthermore, we found that the reconstructed cortical thickness in the region of the brain affected by the

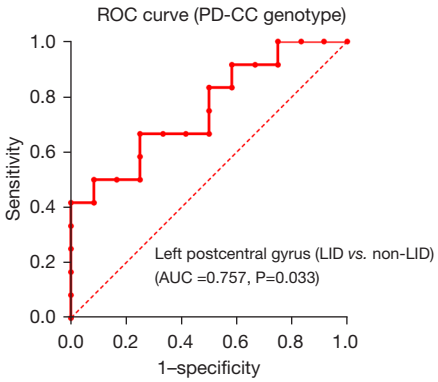

Figure 5 LID identification accuracy of cortical thickness measurements in the region affected by disease status-genotype interaction. In patients with PD and the CC genotype, the cortical thickness of the left postcentral gyrus shows significant potential as an indicator for distinguishing LID and non-LID patients (AUC =0.757, P=0.033). ROC, receiver operating characteristic; AUC, area under the curve; LID, levodopa-induced dyskinesia; PD, Parkinson's disease.

disease status-genotype interaction could be an indicator for distinguishing between patients with and without LID in carriers of the CC genotype. More interestingly, only in the LID-CC group was cortical thickness of the left postcentral gyrus found to be positively associated with the UDysRS score.

BDNF protein can bind to the tropomyosin receptor kinase B (TrkB) and activate the MAPK/ERK, PI3K/PKB, and PLC-γ signal pathways, thus maintaining neuronal survival and improving synaptic plasticity and neurogenesis (6,30). Maladaptive synaptic plasticity might cause LID (31). Previous studies have shown that the *BDNF* rs6265 SNP might affect synaptic plasticity by regulating the secretion of BDNF (6,32). More specifically, it has been shown that the rs6265 CC genotype can upregulate BDNF proteins, while T allele mutations can reduce the levels of BDNF protein by impairing intracellular transport and activity-dependent secretion (7). Leino *et al.* (33) found that BDNF protein levels in the striatum were positively associated with the severity of LID. Therefore, it is necessary to explore the relationship between the *BDNF* rs6265 SNP and LID. In the present study, our findings regarding the region of the brain affected by disease status-genotype interaction and our correlation analysis suggested that the *BDNF* rs6265 SNP might be involved in the progression of LID and affect the function of certain brain regions. Due

to BDNF's neurotrophic effect, BDNF protein levels are usually assumed to be positively correlated with cortical thickness (34). Hence, we speculated that the *BDNF* rs6265 SNP might be associated with maladaptive neural plasticity in LID by regulating BDNF protein levels in the brain, although these levels were not measured in the present study due to the difficulty of sample acquisition.

Our analysis of the primary effects of disease status showed differences in cortical thickness in the right pars orbitalis between the LID and non-LID groups, regardless of the rs6265 genotype. Previous studies have demonstrated that dysfunction of the orbital prefrontal cortex may contribute to dyskinesias (35-37). Cerasa *et al*. (10,11) found that the GM volume and cortical thickness of the inferior frontal gyrus in an LID group were higher than those in a non-LID group. However, no correlation was discovered between the cortical thickness of this brain region and the dyskinesia scale scores in the LID group. Interestingly, considering the influence of the gene, we found that the cortical thickness of the left postcentral gyrus in the LID-CC group was larger than that in the LID-TC/TT group, while there was no significant difference in the non-LID subgroups. Additionally, further analysis showed positive correlations between the cortical thickness in the region of the brain affected by disease status-genotype interaction and UDysRS scores in the LID-CC group. The UDysRS scale is widely used to evaluate the severity of involuntary movements in patients with LID. The higher the score, the more severe the dyskinesia. Therefore, our results suggested that the clinical manifestations of LID might be related to abnormal structural changes in the left postcentral gyrus, which was simultaneously affected by the *BDNF* rs6265 CC genotype. Nevertheless, this genotype appears to be protective, as indicated by a previous discovery by Foltynie *et al*. that the onset of LID in patients with the CC genotype occurs later than in those carrying the T allele (8). These findings are not contradictory to ours, since our study was cross-sectional and the causal relationship between cortical thickness changes and disease status could not be verified. Furthermore, the two studies were based on different indicators; the present study investigated the severity of clinical manifestations, whereas Foltynie *et al*. focused on the symptom onset time. The underlying mechanisms of the effect of the *BDNF* rs6265 SNP on cortical thickness in patients with LID require further longitudinal investigation.

The postcentral gyrus is a crucial somatosensory cortex and plays a vital role in sensorimotor integration. Abnormal sensorimotor integration has been shown to contribute to PD and LID (38). Sensorimotor integration might contain not only striatum and thalamus but also a "cortical loop", where the motor cortex directly receives information from the sensory cortices, such as the primary sensory cortex and the visual cortex (39). Moreover, altered connectivity between the sensory and motor cortices leading to inappropriate information links between input and output pathways of the motor areas has also been associated with LID (31). In a rat model of PD with LID, Alam *et al*. (40) discovered decreased bursting activity of inhibitory neurons in the upper limb sensory cortex, supporting the idea that the somatosensory system contributes to dyskinesia. The same study performed a coherence analysis of the oscillatory activity in the sensory and motor cortices, which suggested that the neuroplasticity of the sensorimotor regulatory network might become impaired after long-term L-dopa treatment. In addition to this, the common pathophysiological mechanisms between pain and dyskinesia found by Sung *et al*. might offer new insight into the role of the sensory pathway in LID (41). The present study demonstrated that interaction between disease status and genotype affected the left postcentral gyrus, and that the cortical thickness in this region was positively correlated with the UDysRS score. Therefore, we speculate that patients with LID have maladaptive sensorimotor integration, which is associated with the severity of their dyskinesia. Admittedly, statistical differences in UDysRS scores were not found between the CC and TC/TT subgroups; this might be a result of our combined analysis of the TC heterozygote and TT homozygote, which was necessary due to our limited sample size.

There were some limitations to the present study. Firstly, changes in BDNF protein levels in patients with PD and LID were not explored in this study, for the difficulty in biochemical assessment of human cerebral cortex. Secondly, due to the small sample size, carriers of the TC and TT genotypes were merged into a single group to ensure the statistical efficiency of the subgroups. It is regrettable that the effects of TC and TT genotypes could not be studied separately. Furthermore, the present study was a cross-sectional study that could not determine a causal relationship between alterations in cerebral cortical thickness and LID, which is something that requires further clarification through longitudinal studies. Participants of this study were randomly enrolled, and the principal results came from objective imaging measurement. Although the above factors ensured relatively good external validity,

the fact that ours was a single-center study may limit the applicability of our results. We anticipate that similar studies including a wider range and larger number of participants will verify our conclusions.

Conclusions

To our knowledge, this is the first study to prove that structural cortical changes to the left postcentral gyrus modulated by the *BDNF* rs6265 SNP are related to the severity of LID and that maladaptive sensorimotor integration of the left postcentral cortex might contribute to the pathogenesis of LID. Our findings provide a new perspective for further exploration of the pathological mechanisms of LID. Furthermore, according to this study, the cortical thickness of the left postcentral gyrus may become a gene-dependent neuroimaging biomarker for identifying LID.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-1018/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1018/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2016-SRFA-094). Informed consent was obtained from all the participants.

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Appendix 1: Clinical assessment

Tinetti test is a reliable and effective tool to evaluate the fall risk of PD patients (42). This assessment consists of two parts, of which 1–9 items are used to evaluate balance ability and 10–16 items are taken to assess gait ability, with a total score of 28 points. The criteria for predicting falling risk are as follows: low fall risk [25–28]; medium fall risk [19–25]; high fall risk (<19).

The Hamilton Anxiety Rating Scale (HAMA) is one of the rating scales to measure the severity of perceived anxiety symptoms. It consists of 14 symptom-defined elements, and each item is scored on a basic numeric scoring of 0 (not present) to 4 (severe) (43): no/minimal anxiety (scores ≤7); mild anxiety [8–14]; moderate anxiety [15–23]; severe anxiety (≥24).

The total score of Hamilton Depression Rating Scale with 24 items (HAMD-24) is 78. Criteria for rating severity of depression are as follows (44,45): no depression [0–7]; mild depression [8–19]; moderate depression [20–34]; and severe depression (≥35).

Mini-Mental State Examination (MMSE) is a simplified cognitive mental status examination, maximum total score of which is 30. Education level is a cardinal demographic factor affecting MMSE score, so the best cut-off point of normal and abnormal cognitive status is determined according to education (46): for illiterate individuals is 17, for individuals with 1–6 years of education is 20, and for individuals with 7 or more years of education is 24. Below the threshold is cognitive impairment, and above is normal.

Frontal Assessment Battery (FAB) consists of 6 items, each with a score of 0–3. The total score ≤12 is defined as significant cognitive impairment (47).

Epworth Sleepiness Scale (ESS) is a brief self-rating scale that can be used to assess daytime sleepiness of PD patients (48). The possibilities of patients dozing off or falling asleep in eight situations are evaluated with a score of 0–3, and the maximum score is 24 points. The score >10 is taken to indicate excessive daytime sleepiness (48,49).

Fatigue severity scale (FSS), a self-questionnaire composed of 9 items, has been widely used to measure fatigue of PD patients. Patients are asked to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicates strongly disagree and 7, strongly agree. The total score > 36 is adopted to indicate the presence of fatigue symptoms (24).

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