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Research Paper

Subcortical structure alteration in patients with drug-induced parkinsonism: Evidence from neuroimaging

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ABSTRACT

Parkinson's Disease (PD) and Drug-induced parkinsonism (DIP) are the most common subtypes of parkinsonism, yet no studies have reported that the subcortical volume alterations in DIP patients. This study aimed to identify specific alterations of subcortical structures volume in DIP patients, and investigate association between the subcortical structure modifications and clinical symptoms. We recruited 27 PD patients, 25 DIP patients and 30 healthy controls (HCs). The clinical symptom-related parameters (Unified Parkinson's Disease Rating Scale, UPDRS) were evaluated. Structural imaging was performed on a 3.0 T scanner, and volumes of subcortical structures were obtained using FreeSurfer software. Analysis of covariance (ANCOVA) and partial correlation analysis were performed. DIP group had significantly smaller volume of the thalamus, pallidum, hippocampus and amygdala compared to HCs. ROC curve analysis demonstrated that the highest area under curve (AUC) value was in the right pallidum (AUC = 0.831) for evaluating the diagnostic efficacy in DIP from HCs. Moreover, the volumes of the putamen, hippocampus and amygdala were negatively correlated with UPDRSII in the DIP patients. The volume of the amygdala was negatively correlated with UPDRSIII. The present study provides novel information regarding neuroanatomical alteration of subcortical nuclei in DIP patients, suggesting that these methods might provide the basis for early diagnosis and differential diagnosis of DIP.

Introduction

Drug-induced parkinsonism (DIP) was the second most common cause of parkinsonism (de Germay et al., 2020), and its incidence increased with older age (Savica et al., 2017). DIP patients often present clinical manifestations similar to Parkinson's disease (PD), such as tremor, myotonia, and bradykinesia, which can lead to misdiagnosis (Esper and Factor, 2008). Despite clinical recognition of DIP as a form of parkinsonism occurring after the use of certain offending drugs, its neuropathological basis remains elusive.

Recent review reported that the dopaminergic radiotracers is currently the most popular neuroimaging techniques in DIP researches. In contrast, there are relatively few MRI studies on DIP, and they primarily focus on brain structural MRI for evaluating the striatal region (Pitton Rissardo and Caprara, 2023). Brain MRI can provide significant benefits for DIP, such as diagnosis, differential diagnosis and evaluation for severity. Lee et al. (2017) found extensive disruption of the white matter microstructure in DIP, and it was correlated with clinical symptoms. Umarov et al. (2016) reported morphological changes in some subcortical nuclei on T2-weighted images in the DIP group with relatively longer illness duration. Sung et al. found that the imaging of nigrosome 1 with 3 T MRI can differentiate DIP from idiopathic Parkinson disease with high accuracy (Sung et al., 2016).

Subcortical nuclei, which includes structures such as the thalamus, basal ganglia, hippocampus and amygdala, play an important role in regulating a variety of physiological and psychological functions in the

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human body, such as motor coordination, metabolic regulation, emotional processing, and cognition, etc. There are many researches about the alterations of subcortical nuclei in PD, which gradually worsens and affects the subcortical nuclei of the basal ganglia, including (McQuade et al., 2021) the caudate nucleus, putamen (collectively known as the striatum), nucleus accumbens, internal and external globus pallidus, substantia nigra, and thalamic nuclei (Lassus et al., 2018). Pitcher et al. (Pitcher et al., 2012) reported that the subcortical research on PD mainly focuses on the striatum, and it is common knowledge that pathophysiological modifications go far beyond the striatum, reaching other subcortical nuclei, such as the thalamus (Del Tredici et al., 2002), and further disruption of the basal ganglia-thalamocortical loops. Structural MRI studies in PD have shown volumetric reductions of subcortical structures such as the thalamus, putamen, globus pallidus, and caudate nucleus(Geevarghese R et al., 2015). Some studies reported the correlation between Unified Parkinson's Disease Rating Scale (UPDRS) motor score and any subcortical structure volume in PD patients (Charroud and Turella, 2021; Geevarghese et al., 2015).

However, until now, no studies have specifically examined subcortical structure volumes in DIP patients or explored correlations with clinical symptoms, such as the UPDRS scores. In DIP patients, the effects of neurotoxic substances on the dopamine pathway (such as neuronal loss, alterations in neurotransmitter levels, etc.) may also lead to changes in subcortical nuclei similar to those observed in patients with PD. To verify this hypothesis, structural MRI may help to elucidate the specific changes occurring in subcortical nuclei in DIP patients. Hence, we conduct our study to explore the alterations in subcortical structure volumes in DIP patients, additionally, investigations into the correlation with clinical symptoms. It not only contributes to a more comprehensive understanding of the subcortical involvement in DIP, but also may provide valuable insights into the neuropathological mechanisms of DIP.

Methods

Subjects

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the Affiliated Hospital of North Sichuan Medical College [No.2021ER0105–1]. These patients/participants provided their written informed consent to participate in this study.

A total of 25 patients with DIP, 27 patients with PD, and 30 healthy control subjects were recruited from Affiliated Hospital of North Sichuan Medical College from March 2021 to December 2022. The diagnosis of PD based on the diagnostic criteria for PD in China (2016 edition) (Group et al., 2016). DIP was diagnosed using the following four criteria: (1) the presence of parkinsonism; (2) no history of parkinsonism prior to the use of the offending drugs; (3) parkinsonism appeared after using pathogenic drugs without a history of Parkinson's disease;(5) right-handed subjects. The exclusion criteria for DIP patients were the following: (1) Primary Parkinson's disease or other clear causes of Parkinson's syndrome;(2) MRI contraindications: claustrophobia, metal implants, and other MRI contraindications;(3) MRI showing obvious structural damage or motion artifact;(4) History of head injury, stroke, or other neurological diseases;(5) Unwilling to participate in this study. The inclusion criteria PD were the following criteria:(1) Meet the clinical diagnostic criteria for PD in China (2016 edition); (2) Willfully participate this research and sign the informed consent document;(3) right-handed subjects. The exclusion criteria for PD patients were the following: (1) Secondary Parkinson syndrome and atypical Parkinson syndrome;(2) Patients who cannot cooperate with the evaluation of motor symptoms and non-motor symptoms; (3) MRI contraindications: claustrophobia, metal implants, and other MRI contraindications; (4) MRI showing obvious structural damage or motion artifact; (5) Unwilling to participate in this study. The age- and sex-matched healthy control were included, and all participants were right-handed. The exclusion criteria for HCs were the following:(1) with history of psychiatric or neurological disease;(2) MRI contraindications: claustrophobia, metal implants, and other MRI contraindications; (3) MRI showing obvious structural damage or motion artifact; (4) Unwilling to participate in this study.

UPDRS score was used to test the clinical symptom. UPDRS III score was used to test motor symptom, while non-motor and motor experiences of daily life were assessed using UPDRS-I and UPDRS-II respectively.

MRI techniques

All MRI data were acquired on a 3.0 T MRI system (GE, Discovery MR750, United States) and with a standard 32-channel head coil. A high-resolution 3D-T1 was used, the parameters were as follows: repetition time (TR) = 8.3 ms, echo time (TE) = 3.3 ms, flip angle = 15°, field of view (FOV) = 240 mm × 240 mm, matrix = 240 × 240, thickness = 1.0 mm, and no gap.

Imaging analysis

FreeSurfer 7.1.1 was used for cortical reconstruction and volumetric segmentation. The automatic segmentation process involves T1-weighted image motion correction, affine registration to the Talairach space, B1 field uniformity correction, skull stripping using a hybrid watershed algorithm, automatic volume labeling, segmentation of subcortical white matter and deep gray matter structures, subcortical structure filling and pruning, construction of a cortical network, etc. Finally, the volumes of 14 subcortical nuclei, including bilateral thalamus, caudate, putamen, pallidum, hippocampus, amygdala and nucleus accumbens were extracted (Fig. 1). Additionally, intracranial volume (ICV) was computed.

Statistical analysis

All continuous variables were presented as the mean or median. Demographic characteristics and UPDRS score were compared using analysis of variance (ANOVA), Mann-Whitney nonparametric U-tests or Chi-Squared test. Analysis of covariance (ANCOVA) was performed using general linear model (GLM) to compare neuroimage parameters among groups and post hoc analysis were performed. P values were corrected for multiple comparisons using false discovery rate (FDR). The correlation between the clinical parameters and subcortical volume were investigated using partial correlation analysis corrected for sex, age and intracranial volume. Receiver operating characteristic (ROC) curve analysis was used to evaluating the sensitivity and specificity of subcortical volume in discriminating DIP from PD and HCs. Statistical analyses were performed using commercially available software (SPSS, Inc., Chicago, IL, Ver. 23.0), and a two-tailed $P < 0.05$ was considered significant.

Result

Demographics

The demographic characteristics of these subject groups are presented in Table 1. There were no significant differences in age, sex distribution, illness duration among the three groups. There are significant differences in UPDRS scores and MoCa scores between the DIP and PD group.

Volumetric analysis

Bilateral thalamus, pallidum, hippocampal and right amygdala showed significant difference among these three groups. Subsequent

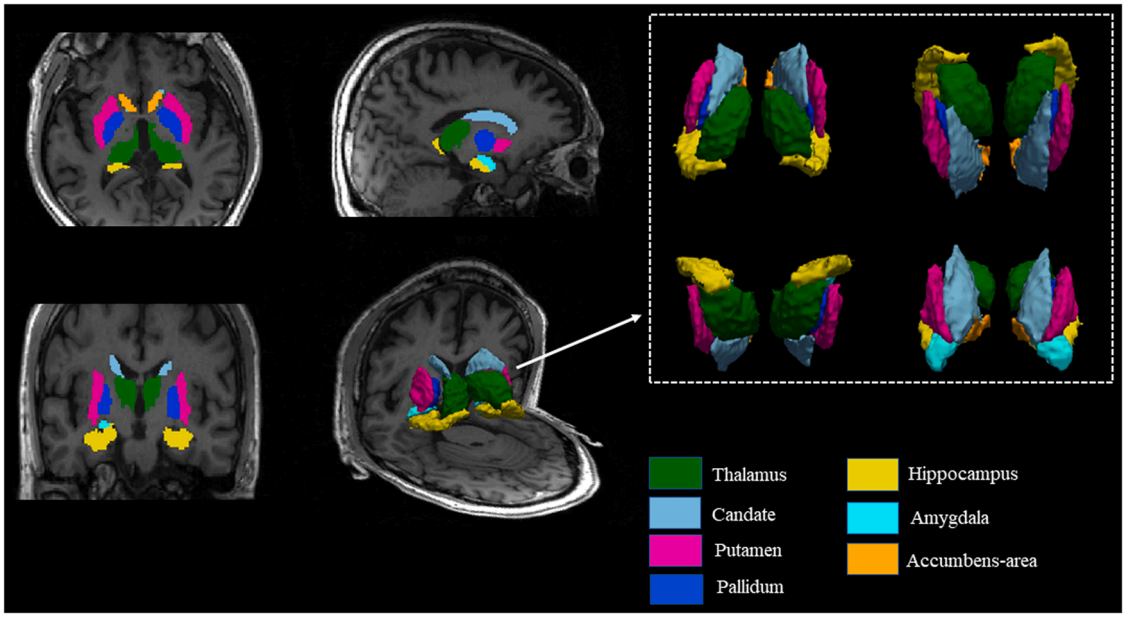

Fig. 1. Example of subcortical nuclei segmentation in a DIP patient.

Table 1
Demographic and clinical information.

N	PD (n=27)	DIP (n=25)	HCs (n=30)	F/z/ x2	p value
age,years,mean(S.D.)	64.70 ±7.93	63.32 ±8.89	62.23 ±5.85	1.025	0.363
sex(m/f)	11/16	10/15	15/15	0.717	0.699
illness duration, year,median (range)	1.0 (0.1–4)	0.7 (0.1–2.6)		-1.795	0.073
URDRS I	8(2–26)	9(1–27)		-0.064	0.949
URDRS II	10 (2–17)	7(1–30)		-0.286	0.037*
URDRS III	17.0 (6–27)	11(5–32)		-0.838	0.005*
MoCa score	18 (0–30)	12(0–27)		-2.736	0.006*
H-Y grading system (N)					
Grade 1	14	10		0.533	0.766
Grade 2	12	13			
Grade 3	1	2			

NOTE: PD, Parkinson's Disease; DIP, Drug-induced parkinsonism; HCs, healthy controls; URDRS, Unified Parkinson's Disease Rating Scale; * indicates $p < 0.05$.

post-hoc test revealed that DIP group had significant smaller volume of the left thalamus, right pallidum, right hippocampus and right amygdala compared to HCs, and the PD group had significant smaller volume of bilateral thalamus, bilateral pallidum, bilateral hippocampal and right amygdala compared to HCs. Moreover, DIP group had a significant volume decrease in bilateral pallidum compared with PD (Table 2 and Fig. 2).

ROC curve analysis discriminating DIP from PD and HCs

For the volume parameters with significant differences among these groups, ROC curve analysis was performed. As shown in Table 3 and Fig. 3, ROC curve analysis demonstrated that the highest area under curve (AUC) value was in the right pallidum (AUC = 0.840) for evaluating the diagnostic efficacy in DIP from HCs (Fig. 3A). And the bilateral pallidum volumes were performed to estimate the potential differential diagnostic value in DIP from PD (Fig. 3B).

The relationship between the subcortical nuclei volume and clinical parameters

Partial correlation analysis was calculated between the subcortical nuclei volume and clinical parameters. In the DIP, the volumes of the bilateral putamen (left: r=-0.689, p<0.001; right: r=-0.677,p=0.004), bilateral hippocampus (left: r=-0.632,p=0.005; right: r=-0.780, p<0.001), and right amygdala (r=-0.661, p=0.004) were negatively correlated with UPDRSII (Fig. 4A). The volumes of the left amygdala were negatively correlated with UPDRSIII (r=-0.578, p=0.023) (Fig. 4B). In the PD, the volumes of the left accumbens was negatively correlated with UPDRSIII (r=-0.609, p=0.028) (Fig. 4C). There is no significant correlation between the volume of subcortical nuclei and illness duration.

Discussion

The present study provides novel information regarding specific neuroanatomical volume change of subcortical nuclei in DIP patients for the first time. The major findings were as follows: DIP patients had significantly smaller volume of the left thalamus, right pallidum, right hippocampus and right amygdala in comparison with HCs, and the volume of left thalamus and right pallidum had better diagnostic performance. The volumes of the bilateral putamen, bilateral hippocampus and right amygdala were positively correlated with UPDRSII and the volumes of the left amygdala were positively correlated with UPDRSIII in DIP group. DIP and PD group mainly exhibited subcortical atrophy in the thalamus, pallidum, hippocampal and amygdala, and these alterations in subcortical nuclei in PD patients influenced more regions than in DIP patients, and the volume of bilateral pallidum had better differential diagnostic value. Our findings suggested the abnormality of subcortical nuclei volume in DIP and PD patients may contribute to the diagnosis or differential diagnosis, and also may provide a basis for exploring the common or specific pathological mechanisms between of the both.

In Parkinson's disease, loss of dopaminergic neurons in the basal ganglia and thalamus can cause the basal ganglia-thalamo-cortical circuitry to malfunction. Components of the limbic and motor systems have been shown to be particularly vulnerable to degeneration. Our results showed that the reduced thalamus and pallidum volume in DIP patients compared to HCs, and the ROC analysis suggested the good diagnostic

Table 2
Volume Differences in the subcortical nuclei Among DIP, PD and HCs.

	PD(N=27)		DIP(N=25)		HCs(N=30)		DIP vs. PD vs. HCs			PD vs. DIP	PD vs. HCs	DIP vs. HCs
	Mean	SD	Mean	SD	Mean	SD	F	P	P.FDR	P.FDR	P.FDR	P.FDR
Left-Thalamus	6549.715	684.615	6074.152	443.565	6595.307	726.966	12.656	0.000*	0.000*	0.070	0.000*	0.026*
Right-Thalamus	6293.489	542.974	5925.600	290.565	6494.903	842.471	8.440	0.000*	0.000*	0.072	0.000*	0.059
Left-Caudate	3566.833	636.900	3426.480	523.077	3066.830	373.681	0.001	0.999	0.999	/	/	/
Right-Caudate	3852.474	720.601	3523.924	532.586	3238.623	428.206	0.943	0.394	0.552	/	/	/
Left-Putamen	4540.274	655.039	4481.132	474.597	4495.813	513.066	0.501	0.608	0.655	/	/	/
Right-Putamen	4680.778	655.756	4666.692	436.402	4625.243	530.009	0.533	0.589	0.655	/	/	/
Left-Pallidum	1873.626	295.872	1657.484	156.625	1938.583	324.915	9.040	0.000*	0.000*	0.028	0.000*	0.166
Right-Pallidum	1842.778	262.154	1625.416	144.539	1887.043	222.105	16.332	0.000*	0.000*	0.021	0.000*	0.026*
Left-Hippocampus	3832.030	433.283	3592.840	624.329	4040.320	292.214	8.059	0.001*	0.003	0.085	0.000*	0.058
Right-Hippocampus	4065.107	439.139	4010.200	443.285	4232.740	393.063	4.530	0.014*	0.028*	0.720	0.004*	0.035*
Left-Amygdala	1461.578	212.275	1408.628	255.556	1506.600	188.947	2.622	0.079	0.123	/	/	/
Right-Amygdala	1677.359	206.609	1622.268	209.913	1697.590	212.162	5.634	0.005*	0.012*	0.720	0.002*	0.026*
Left-Accumbens-area	417.089	90.744	383.856	78.403	464.457	82.165	3.231	0.045*	0.079	/	/	/
Right-Accumbens-area	456.044	85.354	472.172	68.120	448.753	78.219	0.754	0.474	0.603	/	/	/

NOTE: PD, Parkinson's Disease; DIP, Drug-induced parkinsonism; HCs, healthy controls; URDRS, Unified Parkinson's Disease Rating Scale;
* indicates p < 0.05.

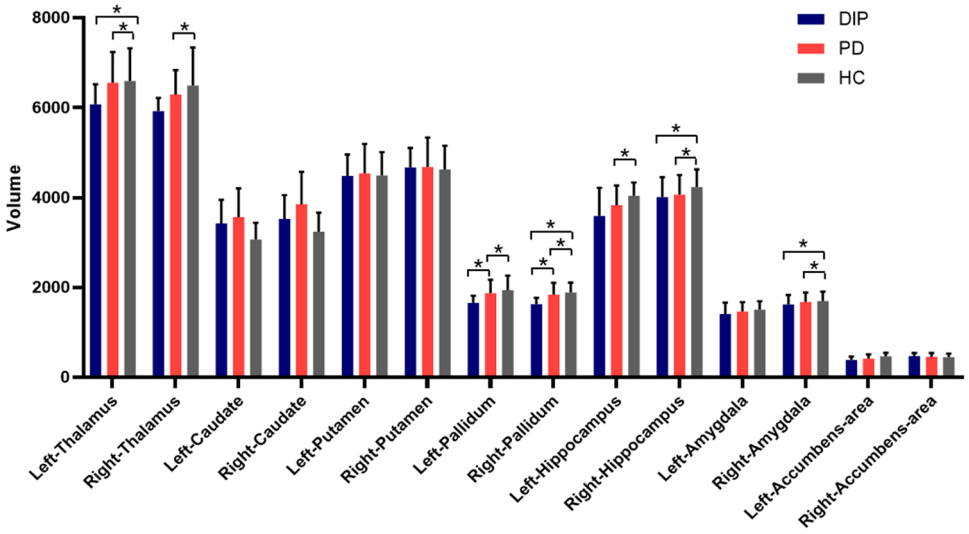

Fig. 2. Volume differences in these subcortical nucleis among those DIP, PD and HCs. * indicates FDR-level significance.

Table 3
ROC Curve Analysis for Differentiating DIP From PD/HCs.

	AUC	95%C.I	Cut-off	Sensitivity	Specificity	P value
DIP vs. HCs						
L_thalamus	0.699	0.560–0.815	6696.600	0.920	0.467	0.005*
R_pallidum	0.840	0.716–0.925	1833.200	0.960	0.767	0.0001*
R_hippocampus	0.624	0.483–0.751	3946.400	0.480	0.867	0.1
R_amygdala	0.569	0.429–0.702	1807.800	0.920	0.333	0.372
DIP vs. PD						
L_Pallidum	0.729	0.588–0.843	1824.600	0.920	0.630	0.001*
R_Pallidum	0.770	0.633–0.875	1696.100	0.800	0.741	0.0001*

NOTE: PD, Parkinson's Disease; DIP, Drug-induced parkinsonism; HCs, healthy controls; ROC, receiver operating characteristic; AUC, area under curve; * indicates p < 0.05.

value. Furthermore, we found that the volumes of hippocampus and amygdala was reduced compared to HCs. This result may be caused by the following two reasons: the one is that the limbic and motor systems are especially prone to degeneration, with specific sites such as the entorhinal region, the second sector of Ammon's horn, and crucial subnuclei of the amygdala being commonly affected (Braak and Braak, 2000). Neuropathological investigations revealed the occurrence of amygdalar and hippocampal degeneration in PD patients with dementia (Cordato et al., 2000). Another reason is that the hippocampus and amygdala, which are core involved in emotional regulation, DIP and PD patients are prone to comorbid emotional disorders (López-Sendón et al., 2013).

Overall, the subcortical nuclei are crucial for regulating a wide range of physiological and psychological functions. They play key roles in motor control, emotional processing, cognitive function, and other essential aspects of human behavior. Our preliminary research findings showed that the thalamus, pallidum, hippocampus and amygdala exhibited volume reduction in DIP patients. We speculate several

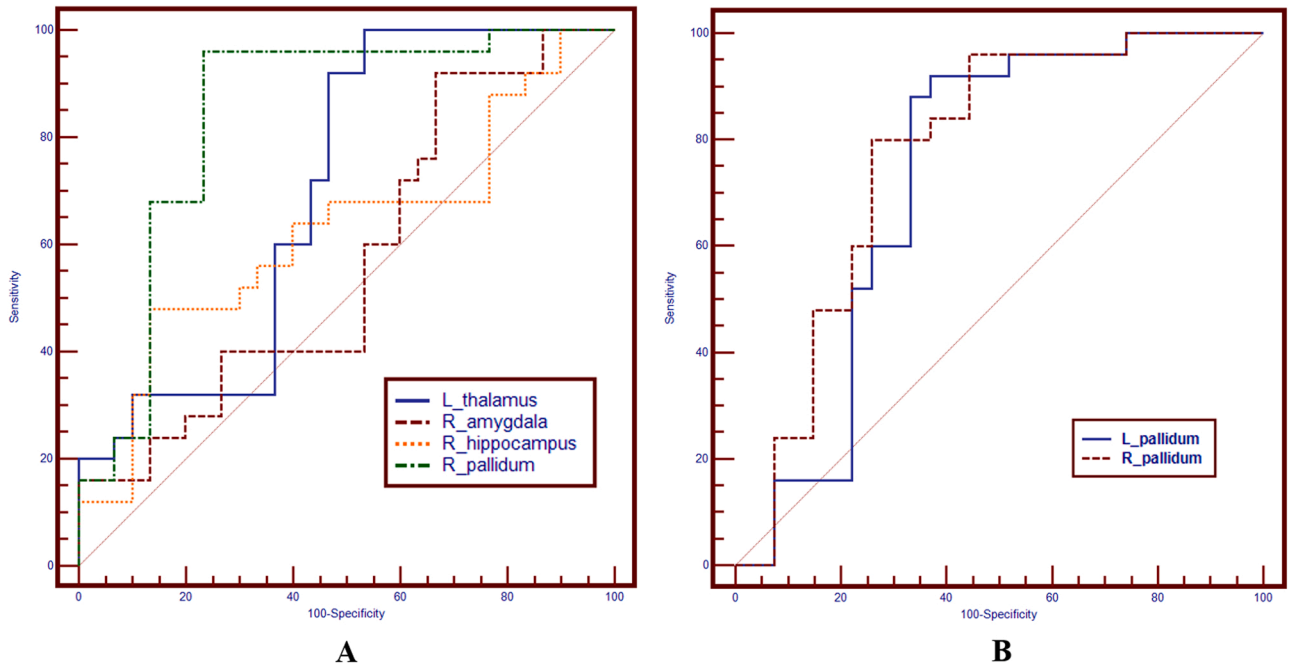

Fig. 3. ROC Curve Analysis of the left thalamus, right pallidum, right hippocampus and right amygdala between DIP and HCs(A); ROC Curve Analysis of bilateral pallidum between DIP and PD(B).

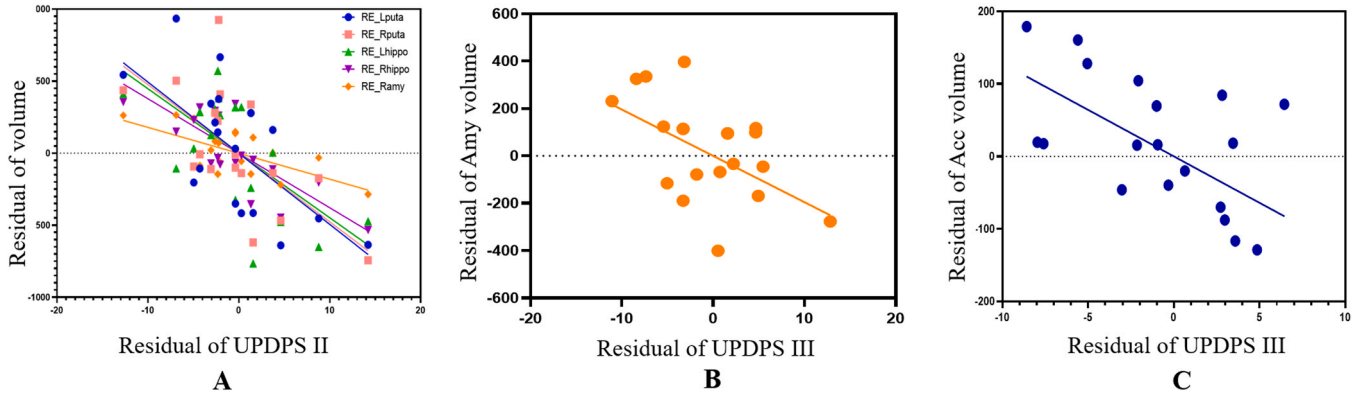

Fig. 4. Correlations between the bilateral putamen/bilateral hippocampus/right amygdala volume and UPDRSII scores in DIP(A). Correlations between the left amygdala volume and UPDRSIII scores in DIP(B). Correlations between the left accumbent volume and UPDRSIII scores in PD(C). All subcortical nuclei volume for the shown were residuals adjusted for age and ICV.

possible reasons as follows. Firstly, the neurotoxic effects of drugs associated with DIP may directly damage dopaminergic neurons within subcortical nuclei. These substances could disrupt cellular processes vital for neuronal survival and function, leading to neuronal loss and subsequent volume reduction in affected regions. Secondly, neurotoxic effects of drugs associated with DIP may disrupt normal neurotransmitter signaling pathways, particularly the dopaminergic system, which plays a crucial role in motor control and coordination. Dysregulation of dopamine signaling can lead to neuronal dysfunction and degeneration in subcortical nuclei, contributing to volume reduction. Additionally, the process of neurodegenerative changes may also contribute to the progression of subcortical nuclei atrophy. Overall, our findings of subcortical nuclei atrophy in DIP patients represent a preliminary discovery, which may result from the complex interaction of factors such as neurotoxicity, neurotransmitter dysregulation, and genetic factors. Further research is needed to elucidate the specific mechanisms underlying subcortical atrophy in DIP and develop targeted interventions to mitigate its progression.

Another interesting finding is that both of the DIP and PD patients had significant smaller volume in the thalamus, pallidum, hippocampus and amygdala, and the difference is that the subcortical alteration in PD is more widely and bilateral. Moreover, the UPDRS III scores is higher in the DIP group than that of PD group (more severe motor disturbances). As a neurodegenerative disorder, PD is marked by the progressive accumulation of a-synuclein (a-syn) in cortical and subcortical regions, which leads to neuronal degeneration resulting in motor dysfunctions and dementia (Trojanowski et al., 1998). The underlying cause of PD is thought to be impaired subcortical motor nuclei (Sidtis and Sidtis, 2018). Previous imaging studies reporting hippocampus (Camicioli et al., 2003; Junqué et al., 2005; Rektorova et al., 2014), amygdala (Junqué et al., 2005; Li et al., 2017) and pallidum atrophy etc. (Charroud and Turella, 2021) in PD patients. On the one hand, our findings may provide a basis for exploring the common pathological mechanisms between DIP and PD. Our results showed the subcortical alteration in PD is more widely and bilateral compared to DIP. We speculated the possible reason is that the DIP is the reversible development of parkinsonian symptoms in patients that are treated with drugs that block the dopaminergic receptor. So the subcortical alteration less than PD. On the

another hand, as we know, DIP is characterized by acute onset, while the PD is chronic. So, we speculate that, under the similar course of the disease (there was no statistical difference in the illness duration between the DIP and PD subjects we included), the motor symptoms of DIP group are less severe than those of PD group.

Partial correlation analysis revealed the different correlation in the DIP group and PD group. In the DIP, we found the smaller volume of bilateral putamen, bilateral hippocampus and right amygdala were negatively correlated with UPDRSII (Fig. 4A), as the same as the correlation of the volumes of the left amygdala with UPDRSIII (Fig. 4B). Left putamen showed the greatest cluster of correlation between regional atrophy and motor scores. UPDRSII and UPDRSIII scores reflected to exercise-related symptoms. The putamen is one of the main projection areas of the striatum, which plays a central role in movement. So, our finding of the alteration of putamen in DIP may be closely related to motor symptoms in DIP. A pathological study has demonstrated that Lewy neurites or α-synuclein stack in the hippocampus of PD patients (Braak et al., 2003; Churchyard and Lees, 1997). In the PD group, we found the volumes of the left accumbens was negatively correlated with UPDRSIII. Previous study showed there is accumulating evidence that non-demented Parkinson's disease is associated with structural changes in the nucleus accumbens at the subcortical level (Mak et al., 2015). Our findings suggested that the nucleus accumbens might be a possible subcortical neural substrate for cognitive impairment and neuropsychiatric symptoms in Parkinson's disease.

This present study had several limitations. First, the present study is cross-sectional. DIP or PD patients may have comorbidities, such as psychotic disorder (Dujardin and Sgambato, 2020) and cognitive confounding both of which could alter the subcortical morphological change. Thus, we could not exclude completely the possibility that different offenders or underlying psychopathology affected subcortical morphometry. Second, our sample sizes were relatively small, which might restrict the generalization of our results and affect our capability to identify correlations between clinical variables and neuroimaging discoveries in this study. Third, the cross-sectional design of this study did not allow us to observe neural changes in DIP and PD with respect to illness progression and treatment response. Additionally, some other factors, such as height, weight, BMI were not recorded, which may have potential implications for our findings. Future studies using larger sample sizes and longitudinal designs are warranted to address these limitations and provide more comprehensive insights into the pathophysiology of DIP.

Conclusion

This study provides the first evidence of subcortical nuclei volume change in patients with DIP, and its severity is correlated with clinical parameters of parkinsonism. These findings indicate that abnormal subcortical nuclei volume may contribute to diagnosing or differentiating DIP and PD patients, and may also provide insight into common or specific pathological mechanisms between the two conditions. Further studies are needed to confirm whether subcortical nuclei volume alterations may be a risk factor for DIP in longitudinal research.

CRediT authorship contribution statement

Conception and design: Wei Zhou, Mengyue Tang, ShuShan Zhang. Provision of study materials or patients: Wei Zhou, Ling Sun, ShuShan Zhang, HongYu Lin, Ying Tan, Yang Fan, Si Fan. Collection and assembly of data: Wei Zhou, Mengyue Tang, Ling Sun, HongYu Lin, Ying Tan, Yang Fan, Si Fan. Data analysis and interpretation: Wei Zhou, Meng Yue Tang, Ling Sun. Manuscript writing and editing: Wei Zhou, Mengyue Tang; ShuShan Zhang. Final approval of manuscript: All authors.

Declaration of Competing Interest

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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