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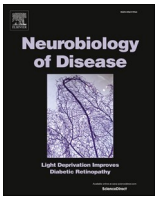

Microstructural alterations of the hypothalamus in Parkinson's disease and probable REM sleep behavior disorder

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ABSTRACT

Background: Whether there is hypothalamic degeneration in Parkinson's disease (PD) and its association with clinical symptoms and pathophysiological changes remains controversial.
Objectives: We aimed to quantify microstructural changes in hypothalamus using a novel deep learning-based tool in patients with PD and those with probable rapid-eye-movement sleep behavior disorder (pRBD). We further assessed whether these microstructural changes associated with clinical symptoms and free thyroxine (FT4) levels.
Methods: This study included 186 PD, 67 pRBD, and 179 healthy controls. Multi-shell diffusion MRI were scanned and mean kurtosis (MK) in hypothalamic subunits were calculated. Participants were assessed using Unified Parkinson's Disease Rating Scale (UPDRS), RBD Questionnaire-Hong Kong (RBDQ-HK), Hamilton Depression Rating Scale (HAMD), and Activity of Daily Living (ADL) Scale. Additionally, a subgroup of PD (n = 31) underwent assessment of FT4.
Results: PD showed significant decreases of MK in anterior-superior (a-sHyp), anterior-inferior (a-iHyp), superior tubular (supTub), and inferior tubular hypothalamus when compared with healthy controls. Similarly, pRBD exhibited decreases of MK in a-iHyp and supTub. In PD group, MK in above four subunits were significantly correlated with UPDRS-I, HAMD, and ADL. Moreover, MK in a-iHyp and a-sHyp were significantly correlated with FT4 level. In pRBD group, correlations were observed between MK in a-iHyp and UPDRS-I.
Conclusions: Our study reveals that microstructural changes in the hypothalamus are already significant at the early neurodegenerative stage. These changes are associated with emotional alterations, daily activity levels, and thyroid hormone levels.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, characterized by various motor and non-motor symptoms(Kalia and Lang, 2015). It involves the progressive degeneration of dopamine neurons, which is primarily attributed to the

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accumulation of pathological α-synuclein protein in the substantia nigra (Bloem et al., 2021; Braak et al., 2003). Furthermore, this pathological α-synuclein extends beyond the substantia nigra, spreading to the basal ganglia, limbic cortex, and much of the neocortex(Braak et al., 2003).

The hypothalamus is positioned in close proximity to the limbic cortex and plays a vital role in numerous essential functions(Müller et al., 2022). These include energy metabolism, regulation of sleep-wake cycles, control of the autonomic nervous system, as well as emotion, and social functions(Hu et al., 2021; Michael and Elmquist, 2020; Ren et al., 2018; Stuber and Wise, 2016). These functions are known to be affected in patients with PD(Berg et al., 2015). Through autopsy studies, evidence of histological involvement of the hypothalamus has been observed in PD patients, as well as in elderly individuals with incidental Lewy pathology, referring to the presence of α-synucleinopathies(De Pablo-Fernandez et al., 2017; Langston and Forno, 1978). However, previous studies examining the relationship between hypothalamic atrophy and PD have yielded conflicting results. Some studies have reported decreased hypothalamic volume in PD and PD with probable rapid-eye-movement sleep behavior disorder (pRBD)(Boucetta et al., 2016; Breen et al., 2016). However, a recent multicenter study suggested that there is no observable atrophy in the hypothalamus of PD patients (Gorges et al., 2019). These discrepancies can be attributed, at least in part, to the challenges associated with hypothalamic segmentation. The lack of image contrast in hypothalamic vicinity, can impede precise volume measurements. Additionally, small sample sizes employed in some studies, coupled with disease heterogeneity within the PD population, can introduce substantial variability.

Given these limitations and discrepancies, the present study aims to address these challenges by adopting a recently developed fully automated deep convolutional neural network-based tool that has demonstrated high accuracy in segmenting the hypothalamus and its subunits from T1-weighted MRI scans(Billot et al., 2020). Additionally, we will incorporate advanced multi-shell diffusion MRI scans to provide complementary information on microstructural changes in the hypothalamus. The use of mean kurtosis (MK), which is a robust biomarker capable of capturing microstructural alterations, will help us detect changes that occur prior to macrostructural atrophy(Bai et al., 2021; Ouyang et al., 2019; Zhu et al., 2021). Furthermore, by utilizing a larger sample size, we can gather more robust and representative data to draw meaningful conclusions.

In this study, we aim to explore the potential association between hypothalamic degeneration and PD, as well as pRBD. Specifically, this study will analyze the degeneration of hypothalamic subunits and investigate their relationship with clinical symptoms and the levels of thyroid hormones (hormones associated with energy metabolism) in individuals diagnosed with PD or pRBD.

2. Materials and methods

2.1. Participants

The dataset included 187 PD, 68 pRBD, and 182 healthy controls, who were recruited from 2015 to 2022. The PD patients were recruited from Department of Neurology, the Second Affiliated Hospital of Zhejiang University School of Medicine and diagnosed by experienced neurologists according to the United Kingdom Parkinson's Disease Society Brain Bank criteria(Daniel and Lees, 1993). The pRBD were recruited from the sleep disorder clinic and defined by the RBD Questionnaire-Hong Kong (RBDQ-HK). Well-matched healthy controls were recruited from the community. All MRI data were visually inspected, and images showing obvious artifacts, cerebrovascular disorders, and intracranial mass were excluded ($n = 5$). Finally, 186 PD, 67 pRBD, and 179 healthy controls were included in this study.

2.2. Clinical and neuropsychological assessments

The Unified Parkinson's Disease Rating Scale (UPDRS) was utilized to assess various domains: Part I was employed for mental examination, Part II for evaluating activity of daily living, and Part III for motor examination. In addition, the Hoehn and Yahr (HY) scale was employed to evaluate motor performance. The presence of RBD symptoms was evaluated using the RBDQ-HK, cognitive function was assessed using the Mini-Mental State Examination (MMSE), mood was measured using the Hamilton Depression Rating Scale (HAMD), and basic functioning in daily activities was evaluated using the Activity of Daily Living (ADL) Scale.

Given the potential overlap in symptoms between PD and thyroid disorders, patients with PD were recommended to undergo thyroid hormone test in this cohort(Kim et al., 2021). A subgroup of patients with PD ($n = 31$) underwent assessment of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels based on their own willing. These individuals had no prior medical history of thyroid disease, and they had not received any anti-thyroid medications or replacement therapy for thyroid hormones. Since participants with pRBD do not have significant motor symptoms, they were not conducted additional thyroid hormone test.

2.3. Magnetic resonance imaging acquisition and processing

2.3.1. Image acquisition

All participants were scanned on a GE Discovery MR750 3.0 T MRI scanner equipped with an eight-channel head coil. High-resolution 3D T1-weighted structural MRI and multi-shell diffusion MRI were acquired. The T1-weighted structural MRI was acquired using the fast spoiled gradient-recalled sequence: echo time (TE) = 3.036 ms; repetition time (TR) = 7.336 ms; inversion time = 450 ms; flip angle (FA) = 11°; field of view (FOV) = 260 × 260 mm^2; matrix = 256 × 256; slice thickness = 1.2 mm. diffusion MRI was acquired with 30 independent diffusion encodings at each shell (b = 1000 and 2000 s/mm^2), and included three acquisitions without diffusion weighting (b = 0). The parameters were as follows: TE = 93.7 ms; TR = 5000 ms; FA = 90°; FOV = 256 × 256 mm^2; matrix = 128 × 128; slice thickness = 4 mm. In addition, an additional b = 0 acquisition with reverse phase-encode polarity was acquired in diffusion MRI data for distortion correction.

2.3.2. Image processing

2.3.2.1. Automated segmentation of hypothalamic subunits using T1-weighted images. The fully automated segmentation method utilized a deep convolutional neural network and employed aggressive data augmentation to enhance the model's robustness to T1-weighted images obtained from diverse sources(Billot et al., 2020). It has been validated on three independent datasets, demonstrating consistent and reliable performance, and reproducible results without requiring any preprocessing steps. The subdivision of the hypothalamus follows the protocol introduced by Makris et al.(Makris et al., 2013). To accommodate the diminutive size of the hypothalamic nuclei, this method employs visible anatomical landmarks to regroup them into five subunits. These subdivisions can be accurately segmented with a standard resolution of 1 mm: anterior-superior (a-sHyp), anterior-inferior (a-iHyp), superior tubular (supTub), inferior tubular (infTub), and posterior (posHyp) subunits by using this fully automated segmentation method(Billot et al., 2020). Specifically, a-sHyp are consist of preoptic area, diagonal band of Broca, sexually dimorphic nucleus of the preoptic area, and paraventricular nucleus; a-iHyp are consist of diagonal band of Broca; nucleus basalis of Meynert; suprachiasmatic nucleus, and supraoptic nucleus; supTub are consist of paraventricular nucleus, dorsomedial nucleus, and lateral hypothalamus; infTub are consist of nucleus basalis of Meynert, supraoptic nucleus, infundibular nucleus, ventromedial

nucleus, nucleus tuberalis lateralis, and tuberomamillary complex; posHyp are consist of mamillary body, lateral hypothalamus; and tuberomamillary complex(Makris et al., 2013). Finally, volumes from the right and the left hemisphere were averaged together, and were adjusted for total incranial volume.

2.3.2.2. Diffusion MRI data preprocessing and hypothalamic signal extraction. Diffusion MRI data preprocessing were conducted using MRtrix3 (v.3.0_RC3, www.mrtrix.org), FMRIB Software Library (v6.0, http://www.fmrib.ox.ac.uk/fsl) and Diffusion Kurtosis Estimator (v.2.6, https://www.nitrc.org/projects/dke/). First, diffusion MRI data were preprocessed via denoising, removing Gibbs ringing artifact. Then, topup and eddy were conducted to correct susceptibility induced distortions, eddy currents, and movements in diffusion MRI data(Andersson and Sotiropoulos, 2016). The skulls were first stripped from the diffusion MRI data for each participant. Finally, the diffusion kurtosis imaging (DKI) derived parameters [MK, axial kurtosis (AK), and radial kurtosis (RK)] were estimated using Diffusion Kurtosis Estimator. MK measurement is the average of AK and RK, and thus only MK measurement is included in next analysis.

To extract the MK measurements in hypothalamic subunits, the b0 maps were linearly registered to the T1 maps, and the MK maps were then transformed to subject T1 space using the transform matrix. To obtain robust mean MK measurements for the hypothalamic subunits, voxel exclusion was performed by excluding ±5% of the voxels with extreme MK values(Shahid et al., 2022). Finally, the averaged MK measurements of left and right hypothalamic subunits were obtained. Summarized steps of the pipeline for imaging processing were shown in Fig. 1.

2.4. Statistical analysis

Comparisons of demographics, clinical and MRI variables between healthy controls, pRBD, and PD were conducted using one-way ANOVA, chi-squared tests, and Kruskal–Wallis tests as appropriate. Partial correlation analysis was used to assess the relationship between MRI variables (volume and MK measurements in hypothalamic subunits) and clinical variables in PD and pRBD, respectively. Age and sex were considered as covariates of no interest. False discovery rate (FDR) was performed for multiple comparison correction, and a two-tailed $p < 0.05$ was considered significant.

In PD subgroup analysis, partial correlation analysis was conducted to assess the relationship between MK measurements of hypothalamic subunits and the levels of TSH, FT3, and FT4, while accounting for age and sex as covariates of no interest.

3. Results

There were no significant differences observed in terms of age, sex, and level of education among the healthy controls, individuals with pRBD, and PD. Significant differences were observed in the scores of UPDRS-I, UPDRS-II, UPDRS-III, RBDQ-HK part I, RBDQ-HK part II, HAMD, ADL, and MMSE scores among the three groups ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.004$, and $p = 0.048$ respectively). Detailed post hoc results were described in Table 1.

The volume measurements of five hypothalamic subunits were not significantly different among the three groups (Fig. 2A). The MK measurement in four hypothalamic subunits, including a-sHyp, a-iHyp, supTub, and infTub, showed significant differences among the three

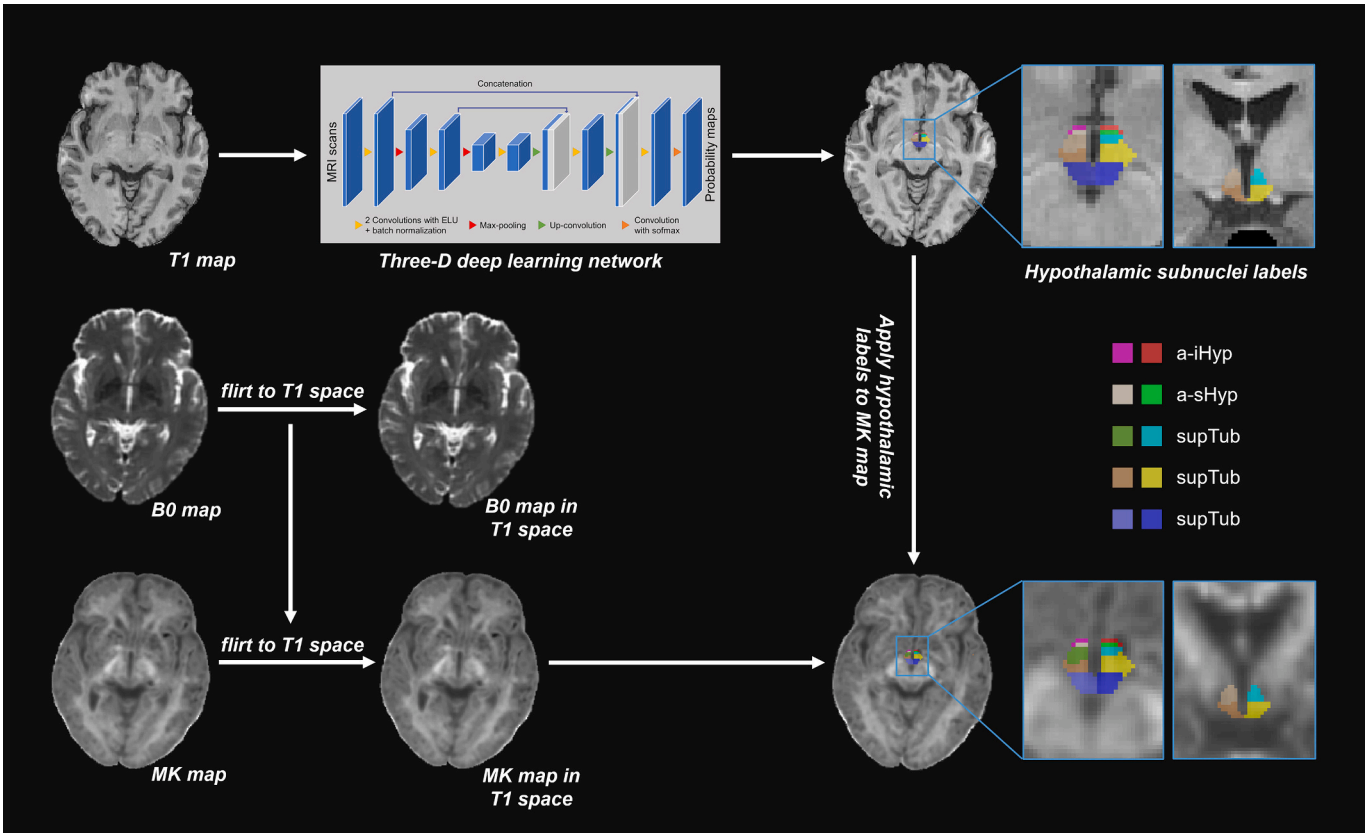

Fig. 1. Summarized steps of the pipeline for imaging processing. The subdivision of the hypothalamus is conducted by the fully automated segmentation method utilizing a deep convolutional neural network. Five subunits including anterior-superior (a-sHyp), anterior-inferior (a-iHyp), superior tubular (supTub), inferior tubular (infTub), and posterior (posHyp) are obtained in the native T1 space. By using FMRIB Software Library v6.0, the b0 map is affine aligned to the native T1 map, and the MK map is aligned to the native T1 map by using the transformation matrix. Finally, the mean MK values of hypothalamic subunits are obtained. a-sHyp: anterior-superior; a-iHyp: anterior-inferior; supTub: superior tubular; infTub: inferior tubular; posHyp: posterior hypothalamus.

Table 1
Participant's characteristics.

	Healthy control ($n = 179$)	Probable RBD ($n = 67$)	Parkinson's Disease ($n = 186$)	p_{anova}	p_a	p_b	p_c
Sex (male/female)	89/90	35/32	109/77	0.226	–	–	–
Age (years)	62.39 ± 7.1	62.81 ± 7.09	61.97 ± 7.33	0.691	–	–	–
Education (years)	9.51 ± 3.17	8.85 ± 2.72	9.25 ± 3.03	0.306	–	–	–
Duration (years)	–	–	3.79 ± 2.95	–	–	–	–
UPDRS-I	0.54 ± 0.78	1.39 ± 1.82	1.45 ± 1.49	<0.001	<0.001	<0.001	0.790
UPDRS-II	0.51 ± 1.03	1.85 ± 2.65	8.7 ± 4.97	<0.001	<0.001	<0.001	<0.001
UPDRS-III	0.86 ± 1.82	3.3 ± 3.57	21.87 ± 12.21	<0.001	<0.001	<0.001	<0.001
Hoehn-Yahr stage	–	–	2.14 ± 0.59	–	–	–	–
RBDQ-HK part I	6.79 ± 5.05	14.12 ± 4.98	9.05 ± 5.78	<0.001	<0.001	0.001	<0.001
RBDQ-HK part II	2.55 ± 4.04	22.63 ± 10.76	9.95 ± 10.28	<0.001	<0.001	0.001	<0.001
MMSE	27.86 ± 2.17	27.15 ± 2.58	27.37 ± 2.53	0.048	0.052	0.031	0.488
HAMD	2.39 ± 3.41	4.77 ± 3.82	6.14 ± 5.12	<0.001	<0.001	0.005	0.111
ADL	20.01 ± 0.11	20.01 ± 0.12	21.01 ± 4.32	0.004	0.006	0.908	0.007

RBD: rapid eye movement sleep behavior disorder; LEDD: levodopa equivalent daily dose; UPDRS: the Unified Parkinson's Disease Rating scale; RBDQ-HK: Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire, Chinese University of Hong Kong version; HAMD: Hamilton Depression Scale; MMSE: Mini-Mental State Examination; ADL: Activity of Daily Living; p_{anova}: Healthy control vs Parkinson's Disease vs Probable RBD; p_a: Healthy control vs Parkinson's Disease; p_b: Healthy control vs Probable RBD; p_c: Parkinson's Disease vs Probable RBD.

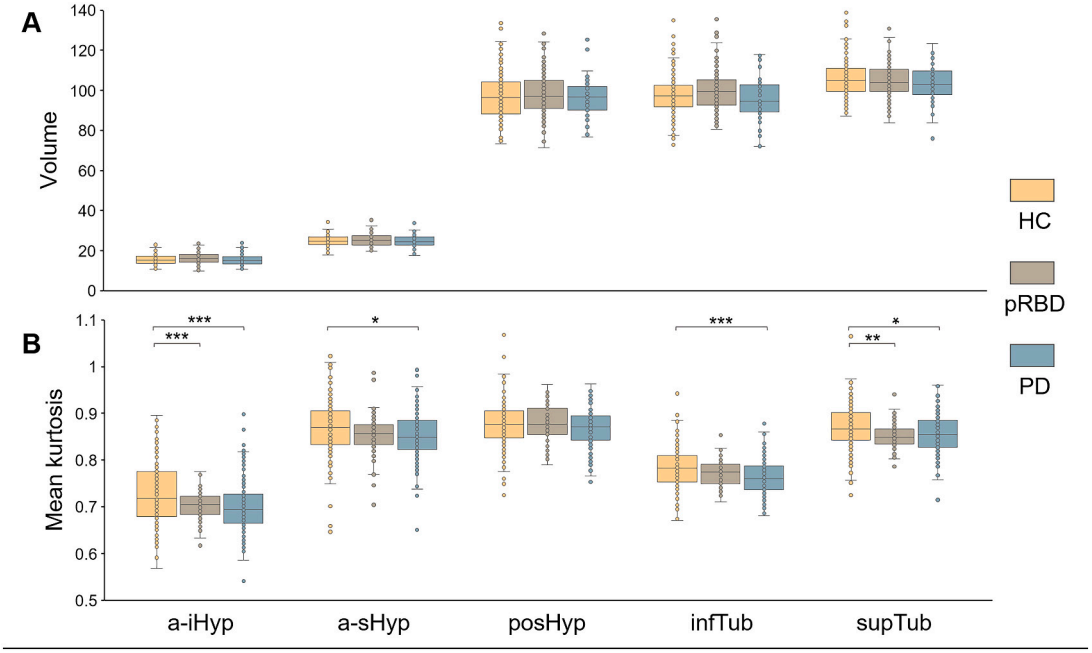

Fig. 2. Comparison of the volume and MK measurements in hypothalamic subunits among three groups. (A) No significant difference was found in the volume of hypothalamic subunits among the three groups; (B) PD exhibited significantly decreased MK measurements in a-sHyp, a-iHyp, supTub, and infTub when compared with HC; and pRBD exhibited significantly decreased MK measurements in a-iHyp and supTub when compared with HC. Boxplots displaying the median as the center, the 25% and 75% quartiles as the bounds of the box, and the Q3 + 1.5 × IQR/Q1–1.5 × IQR as the whiskers.
HC: healthy control; pRBD: probable rapid-eye-movement sleep behavior disorder ; PD: Parkinson's Disease; MK: mean kurtosis; a-sHyp: anterior-superior; a-iHyp: anterior-inferior; supTub: superior tubular; infTub: inferior tubular; posHyp: posterior hypothalamus. *Corrected $p < 0.05$; **corrected $p < 0.01$; ***corrected $p < 0.001$.

groups ($p < 0.001$, $p = 0.015$, $p < 0.001$, and $p = 0.003$, respectively, FDR corrected, Fig. 2B). Specifically, PD exhibited significantly decreased MK in a-sHyp, a-iHyp, supTub, and infTub when compared with healthy controls ($p < 0.001$, $p = 0.013$, $p < 0.001$, and $p = 0.013$, respectively, FDR corrected); and pRBD exhibited significantly decreased MK in a-iHyp and supTub when compared with healthy controls ($p < 0.001$ and $p = 0.004$, respectively, FDR corrected); no significant difference in MK measurements between PD and pRBD was detected after FDR correction.

Correlation analysis was conducted to examine the relationship between MK measurements (a-sHyp, a-iHyp, supTub, and infTub) and clinical assessments, revealing significant differences in inter-group analysis. In the PD group, a negative correlation was observed between MK in infTub and UPDRS-I score ($r = -0.183$, $p = 0.048$, FDR corrected). Additionally, MK in a-sHyp, supTub, and infTub showed negative correlations with HAMD score ($r = -0.208$, $p = 0.012$; $r = -0.205$, $p = 0.012$; $r = -0.160$, and $p = 0.043$, respectively, FDR corrected, Fig. 3). Furthermore, MK in a-sHyp, infTub, and supTub exhibited negative correlations with ADL score ($r = -0.226$, $p = 0.005$; $r = -0.194$, $p = 0.017$; $r = -0.312$, and $p < 0.001$, respectively, FDR corrected) in the same group. In the pRBD group, a significant correlation was found between MK in a-iHyp and HAMD score ($r = -0.307$, $p = 0.022$, FDR corrected).

In addition, among PD patients who underwent the assessment of thyroid hormones ($n = 31$, 13 female, age = 61.85 ± 6.73, level of education = 9.44 ± 2.56), significant correlations were found between the

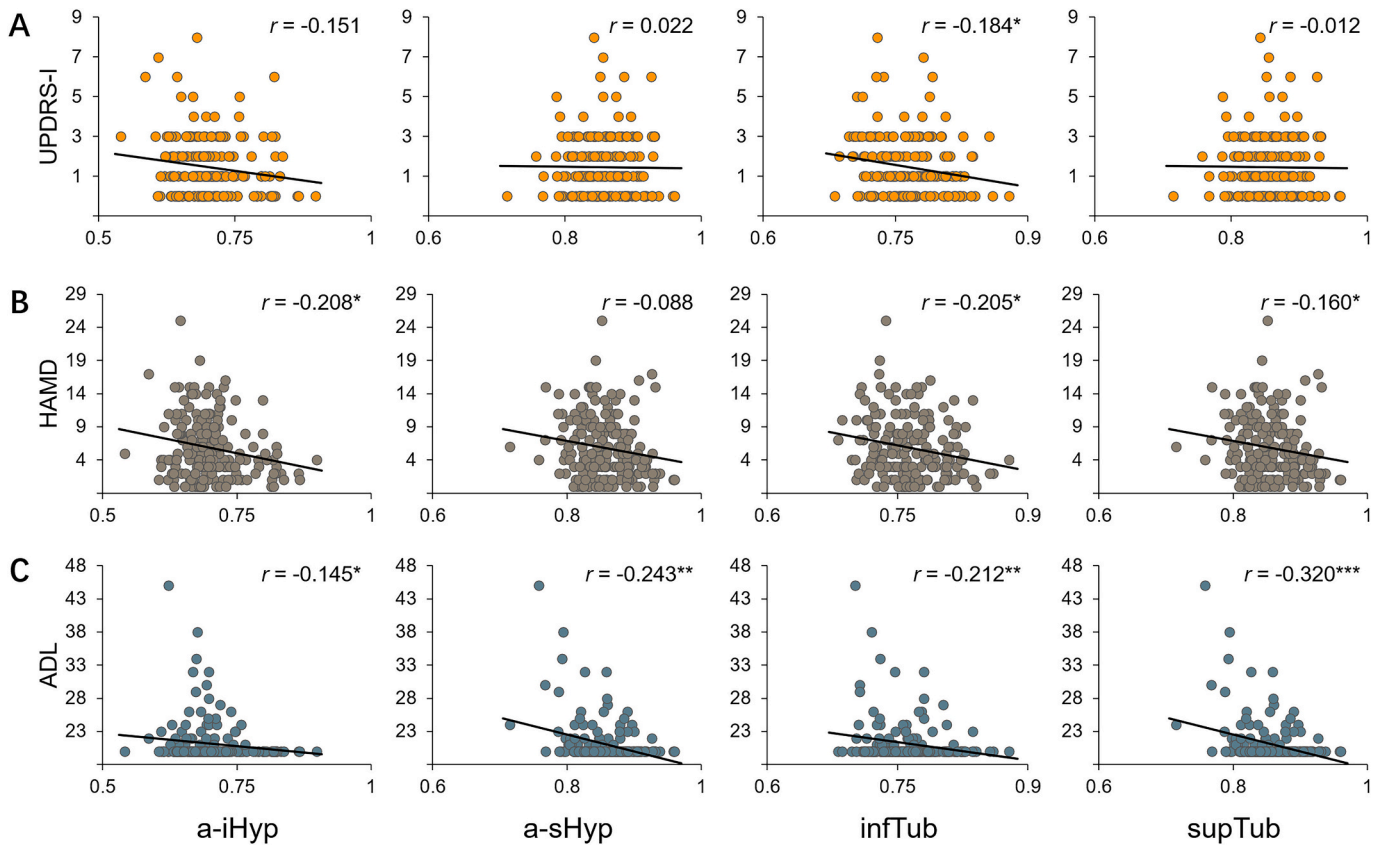

Fig. 3. The relationships of microstructural degeneration in hypothalamic subunits and clinical assessments in PD group. (A) MK measurement of infTub correlated with UPDRS-I score; (B) MK measurements of a-sHyp, supTub, and infTub correlated with HAMD score; (C) MK measurements of a-sHyp, infTub, and supTub correlated with ADL score.
PD: Parkinson's Disease; MK: mean kurtosis; a-sHyp: anterior-superior; a-iHyp: anterior-inferior; supTub: superior tubular; infTub: inferior tubular hypothalamus. UPDRS-I: part I of the Unified Parkinson's Disease Rating scale; HAMD: Hamilton Depression Scale; ADL: Activity of Daily Living. *Corrected $p < 0.05$; **corrected $p < 0.01$; ***corrected $p < 0.001$.

FT4 level and the MK in a-iHyp and a-sHyp ($r = 0.455$, $p = 0.013$ and $r = 0.399$, $p = 0.032$, respectively, uncorrected, Fig. 4).

4. Discussion

In this study, we sought to investigate the extent of degeneration in the hypothalamus and its subunits in a large cohort diagnosed with PD or pRBD. We utilized a novel fully automated segmentation tool to accurately quantify this degeneration(Makris et al., 2013). Our findings reveal significant microstructural degeneration within the hypothalamic subunits of both PD and pRBD subjects using multi-shell diffusion MRI. Importantly, these degenerative changes were associated with emotional disturbances, declines in basic daily functioning, and lower thyroxine levels. Collectively, our results provide evidence for the involvement of hypothalamic degeneration in the clinical symptoms in individuals with PD and pRBD.

Our study did not find significant atrophy in the hypothalamic subunits in either PD or pRBD, which is consistent with a previous study suggesting the absence of detectable macroscopic structural changes in the hypothalamus(Gorges et al., 2019). However, our study did reveal a decrease in MK in multiple hypothalamic subunits in both PD and pRBD. MK is an effective biomarker for quantifying microstructural alterations associated with the deposition of pathological proteins, such as α-synuclein and tau, which lead to a decrease in dendritic and axonal density and subsequent neuronal death(Fathy et al., 2022; Prots et al., 2018; Zhu et al., 2021). Our previous research has demonstrated that MK is a sensitive measure for detecting microstructural changes in early-stage PD, which can be observed before macrostructural atrophy becomes apparent(Bai et al., 2021). Furthermore, our analysis of hypothalamic subregions indicates that hypothalamic degeneration does not follow a specific pattern of progression, as observed in the substantia nigra, but rather appears as a diffuse injury(Biondetti et al., 2020). This may be due to the relatively small size of the hypothalamus, as pathological α-synuclein can quickly affect the entire hypothalamus rather than being localized to a specific subregion. In brief, our findings provide evidence that microstructural alterations in the hypothalamus is detectable in patients with PD and even in individuals with pRBD. However, it should be point out that we did not find a significant correlation between RBDQ-HK scores and hypothalamic MK values in both PD and pRBD groups. Given that degeneration of the hypothalamus is not a primary aspect of PD but part of its intricate degenerative process, it explains why there's no significant correlation between hypothalamic degeneration and the severity of RBD.

The hypothalamus is an important component of the hypothalamic-pituitary-adrenal (HPA) axis, impacting various physiological functions (Nemeroff, 1989). Dysregulation of HPA axis can lead to disorders like depression(Mendoza and Hollenberg, 2017; Nemeroff, 1989). Recent study imply that hypothalamic stimulation can induce feelings of sadness(Parvizi et al., 2022). In this study, we found that decreased MK measurements in specific hypothalamic regions were associated with depressive symptoms in PD patients. These regions correspond to the anatomical locations of the nuclei involved in the HPA axis, such as the paraventricular nucleus and lateral hypothalamic area. These findings suggest that hypothalamic degeneration may be one of the underlying mechanisms contributing to depressive symptoms in PD.

Moreover, we found a significant correlation between hypothalamic

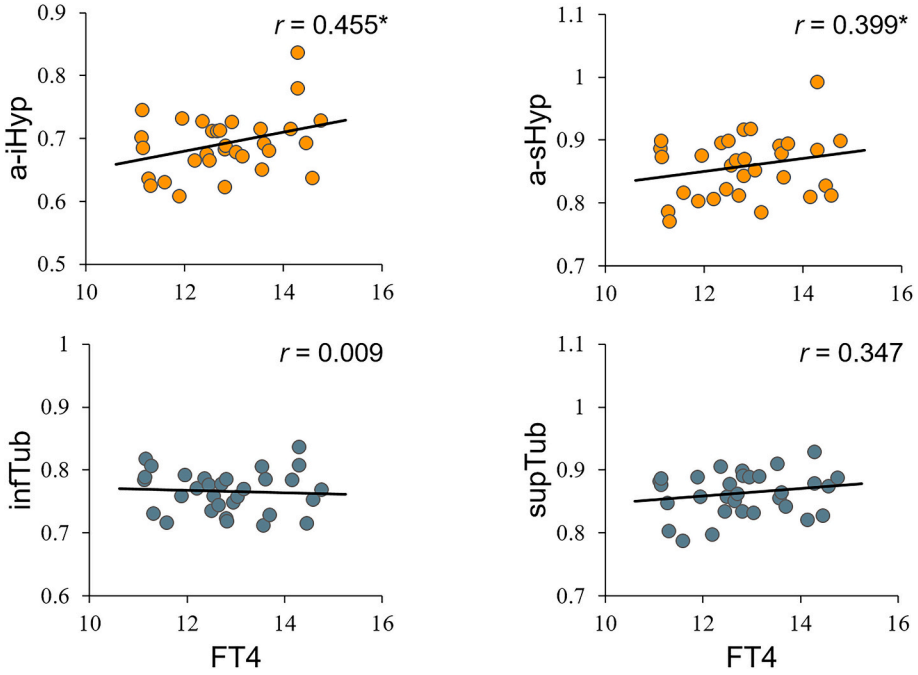

Fig. 4. The relationships of microstructural degeneration in hypothalamic subunits and FT4 level in PD group. Thirty-one PD patients underwent assessment of FT4 levels. MK measurements of a-iHyp and a-sHyp correlated with FT4 level.
PD: Parkinson's Disease; MK: mean kurtosis; a-sHyp: anterior-superior; a-iHyp: anterior-inferior; supTub: superior tubular; infTub: inferior tubular hypothalamus. FT4: free thyroxine. *Corrected $p < 0.05$; **corrected $p < 0.01$; ***corrected $p < 0.001$.

degeneration and worsened performance in basic daily functions. While previous research has not directly linked hypothalamic degeneration to ADL, there is a strong association between hypothalamus and frailty, which reflects impaired basic functioning in daily activities(Chen et al., 2021; Clegg and Hassan-Smith, 2018). Hormonal systems regulated by the hypothalamus, including glucocorticoid secretion, insulin-like growth factor signaling, and androgen production, have been shown to be related to unfavorable aging profiles and frailty(Cappola et al., 2009; Clegg and Hassan-Smith, 2018). Furthermore, the hypothalamus plays a role in modulating factors such as emotions, temperature, and metabolic balance, all of which can impact ADL(Gui and Zhou, 2021; Wang et al., 2023; Yu et al., 2023). These factors may contribute to the observed correlation between hypothalamic degeneration and impaired basic functioning in daily activities. Consequently, our findings suggest that interventions targeting the hypothalamus may have the potential to improve the quality of life among individuals with PD.

Finally, we observed a significant correlation between MK in specific hypothalamic regions (a-iHyp and a-sHyp, including the paraventricular nucleus) and FT4 levels in a small group of patients with PD. The synthesis and secretion of thyroid hormones are regulated by the hypothalamus(Mendoza and Hollenberg, 2017). Disruption to the hypothalamus can impair the production and release of thyrotropin-releasing hormone and thyroid-stimulating hormone, resulting in reduced thyroid hormone secretion(Mendoza and Hollenberg, 2017; Tan et al., 2021). This study suggest that hypothalamic degeneration might contribute to abnormality of FT4 levels in individuals with PD. However, due to the small sample size in our study, the observed associations between MK in hypothalamic regions and FT4 levels did not retain statistical significance after adjusting for multiple comparisons. Therefore, it is important to interpret these findings with caution.

This study has several limitations. Firstly, the lower resolution of diffusion MRI compared to structural MRI may introduce partial volume effects that could impact the precision of MK measurements. However, the use of a large sample size in this study helps mitigate potential errors to some extent. Secondly, the diagnosis of pRBD in our study relied solely on scale assessments, which may increase the possibility of false-positive cases when compared to RBD confirmed through polysomnography. Consequently, the findings related to RBD should be interpreted with caution. Thirdly, the association between hypothalamic degeneration and decreased thyroxine levels did not withstand multiple comparison correction. Therefore, it is essential to interpret these findings regarding thyroxine levels with caution. Lastly, nearly half of the individuals in our pRBD cohort are female, which deviates from the epidemiological feature of PD being more commonly found in males. We speculate that this could be due to women being more attentive to health issues and more likely to seek medical attention, thereby leading to a selection bias in our sample(Lim et al., 2019).

5. Conclusion

This study provides evidence that detectable microstructural alterations in the hypothalamus during the early neurodegenerative stage. Additionally, our findings suggest that microstructural alteration in hypothalamic are associated with emotional alterations, daily activity levels, and thyroid hormone levels. These findings demonstrate that hypothalamus might be a potential target for adjuvant therapeutic approaches in the management of PD.

Research ethics and patient consent

The study was conducted in accordance with the Declaration of Helsinki. The protocol, consent form, and other relevant documentations were approved by the local ethics committee before the study commenced. All participants provided the written informed consent before enrollment.

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CRediT authorship contribution statement

Cheng Zhou: Conceptualization, Methodology, Formal analysis, Writing — Original draft preparation, Visualization, Investigation, Funding acquisition. **Jia You:** Writing – review & editing, Project administration, Methodology, Formal analysis. **Xiaojun Guan:** Writing — review & editing, Data curation, Visualization, Investigation, Funding acquisition. **Tao Guo:** Writing – review & editing, Resources, Project administration, Funding acquisition, Data curation. **Jingjing Wu:** Writing – review & editing, Resources, Data curation. **Haoting Wu:** Writing – review & editing, Resources, Data curation. **Jingwen Chen:** Writing – review & editing, Data curation. **Jiaqi Wen:** Resources, Data curation. **Sijia Tan:** Data curation. **Xiaojie Duanmu:** Data curation. **Jianmei Qin:** Data curation. **Peiyu Huang:** Writing – review & editing, Funding acquisition. **Baorong Zhang:** Resources, Data curation. **Wei Cheng:** Writing – review & editing, Data curation. **Jianfeng Feng:** Supervision, Funding acquisition. **Xiaojun Xu:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Linbo Wang:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Minming Zhang:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author (i.e., Minming Zhang) on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2024.106472.

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