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Olfactory Dysfunction as a Window Into the Heterogeneity of Parkinson Disease

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ABSTRACT

Background: While olfactory dysfunction is common in Parkinson disease (PD), its neural basis and clinical implications remain to be clarified. We investigated the neural substrates and clinical profiles, particularly non-motor symptoms (NMSs), associated with olfactory function.

Methods: This retrospective study included 259 drug-naïve patients with PD who underwent the Cross-Cultural Smell Identification Test (CC-SIT), comprehensive autonomic function test, neuropsychological assessments, and the Neuropsychiatric Inventory Questionnaire (NPI-Q) at diagnosis. NMS profiles were compared across olfactory groups defined by CC-SIT scores (normosmia [$n = 45$], hyposmia [$n = 143$], anosmia [$n = 74$]). Associations between olfaction and clinical/imaging variables were assessed using correlation and path analyses. Cox proportional hazards models were employed to evaluate the risk of developing motor complications or PD dementia according to olfactory status.

Results: CC-SIT scores correlated with Composite Autonomic Severity Scale scores ($\rho = -0.219$, $p = 0.001$), NPI-Q scores ($\rho = -0.269$, $p < 0.001$), and cognitive performance in memory ($\rho = 0.288$, $p < 0.001$) and frontal/executive domains ($\rho = 0.205$, $p = 0.001$). Dopaminergic depletion in the caudate nucleus and limbic atrophy emerged as neural substrates underlying olfactory dysfunction, mediating the association between olfaction and cognitive/neuropsychiatric symptoms. Anosmia was associated with increased risk of developing PD dementia compared to normosmia (hazard ratio [HR]: 2.579; 95% confidence intervals [CI]: 1.137–5.851) and hyposmia (HR: 2.783; 95% CI: 1.437–5.390). Anosmia was associated with higher risk of developing freezing of gait (HR: 2.571; 95% CI: 1.077–6.134) compared to normosmia.

Conclusions: Olfactory dysfunction serves as a multifaceted clinical marker associated with convergent degeneration of nigrostriatal and limbic pathways, offering insights into PD phenotypic variance and its prognostic implications.

1 | Introduction

Parkinson disease (PD) is recognized as a multi-systemic disorder characterized not only by classic motor features, but also by a broad spectrum of non-motor symptoms (NMSs), including

rapid eye movement sleep behavior disorder (RBD), dysautonomia, cognitive impairment, and olfactory dysfunction [1]. Among these, olfactory dysfunction is a highly prevalent NMS in PD that often predates motor symptom onset by years, sometimes over a decade [2–4]. However, olfactory dysfunction is not

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universal among PD patients and demonstrates considerable heterogeneity. In approximately 10%–25% of PD cases, olfaction remains preserved at diagnosis (normosmia), while others present with varying degrees of impairment, exhibiting reduced function (hyposmia) or a complete loss of smell (anosmia) [4, 5].

Impaired olfaction is associated with a wide variety of other NMSs, including dysautonomia, RBD, cognitive impairment, and neuropsychiatric symptoms (NPSs) in PD [6–13]. Accumulating evidence suggests that the degree of olfactory dysfunction at disease onset may be associated with distinct clinical phenotypes characterized by different patterns of disease progression and cognitive decline in PD [12–14]. However, the mechanisms underlying the association between olfaction and clinical heterogeneity in PD, as well as the neural substrates of olfactory impairment, remain poorly understood. While some studies have implicated presynaptic dopaminergic degeneration as a potential mechanistic link [15–17], the dopaminergic system alone may be insufficient to fully account for the multifaceted role of olfaction in the phenotypic diversity of PD [18–20].

Recently, subtyping PD based on NMS profiles has gained attention for its potential to more comprehensively characterize disease phenotypes, given their association with the distribution or spreading pattern of synucleinopathy [1, 21–23]. In particular, the body-first and brain-first subtypes, conceptualized through NMS profiles and supportive biomarkers, have substantially advanced our understanding of distinct α -synuclein origins and their subsequent propagation [21–23]. However, whether olfactory dysfunction represents a brain-first or body-first feature remains contentious [9, 21–23], with some studies associating impaired olfaction with features of brain-first PD [24–27], whereas others link it to RBD or dysautonomia, consistent with a body-first phenotype. This uncertainty underscores the need for comprehensive investigation of olfactory dysfunction in the context of its associated NMS profiles.

To address these knowledge gaps, the present study included drug-naïve patients with PD who underwent comprehensive assessments of NMS at baseline, thereby minimizing potential masking or alleviating effects of dopaminergic medications. Specifically, we aimed to (1) characterize the NMS profiles associated with olfactory dysfunction; (2) identify neural substrates of olfactory dysfunction using dopamine transporter (DAT) imaging and structural magnetic resonance (MR) imaging; (3) assess whether these substrates mediate the relationship between olfactory function and associated NMSs; and (4) explore whether baseline olfactory function holds prognostic value for motor and cognitive outcomes.

2 | Methods

2.1 | Study Population

A total of 259 consecutive drug-naïve PD patients were included in the study, all of whom visited the Movement Disorders Clinic at Severance Hospital between June 2015 and June 2024. PD was diagnosed according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank. All patients completed ^{18}F N-(3-fluoropropyl)-2 β -carbon

ethoxy-3 β -(4-iodophenyl) nortropane (^{18}F -FP-CIT) positron-emission tomography (PET), structural MR imaging (MRI), the Cross-Cultural Smell Identification Test (CC-SIT), AFTs, standardized neuropsychological assessments, RBD Screening Questionnaire (RBDSQ), Non-Motor Symptom Questionnaire (NMSQ), and Neuropsychiatric Inventory Questionnaire (NPI-Q), at baseline. All patients exhibited decreased uptake on ^{18}F -FP-CIT PET in the posterior putamen, and their sustained responsiveness to dopaminergic medications was confirmed by two movement disorder specialists (Y.H.S. and P.H.L.) during the follow-up period (mean 55.1 ± 32.8 months).

We excluded patients with (1) other neurologic disorders, including epilepsy or stroke, (2) unexplained structural brain lesions observed in MRI, (3) poor responsiveness to anti-parkinsonian therapy or features suggestive of atypical parkinsonism, and (4) conditions affecting olfactory (e.g., sinusitis) or autonomic function (e.g., autoimmune diseases, heart failure, or arrhythmia).

The cognitive status of our study participants was determined according to the Movement Disorder Society Task Force guidelines [28]. Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III. Motor subtypes were determined based on UPDRS scores, as previously described (Method S1) [29].

This study was approved by the institutional review board of Yonsei University Severance Hospital (4-2024-3302). Informed consent was waived due to the retrospective nature of the study.

2.2 | Assessment of Olfactory Function

Olfactory function was assessed using the CC-SIT, consisting of 12 odor identification items [30]. Each odor was presented to the patients, and they were asked to select the most appropriate response among four options (total score: 0–12). Based on scores, participants were categorized into anosmia (0–4), hyposmia (5–8), and normosmia (9–12).

2.3 | Assessment of Autonomic Function

Comprehensive autonomic function tests (AFT) were performed to evaluate sudomotor (Quantitative Sudomotor Axon Reflex Test), cardiovagal (heart-rate response to deep breathing, as well as the Valsalva ratio), and adrenergic function (beat-to-beat blood pressure measurements during the Valsalva maneuver and the head-up tilt test) [31]. The Composite Autonomic Severity Scale (CASS) total scores (0–10) and their subdomain scores (sudomotor, 0–3; cardiovagal, 0–3; adrenergic, 0–4) were calculated as previously described [31], with dysautonomia severity graded as none/mild (0–3), moderate (4–6), or severe (7–10).

2.4 | Assessment of Cognitive and Neuropsychiatric Symptoms

A standardized neuropsychological assessment, the Seoul Neuropsychological Screening Battery, was administered to evaluate the cognitive status [32, 33]. Domain-specific scores

were calculated by averaging age-/education-normalized standardized z-scores from quantifiable subtests within each cognitive domain.

The NPS burden was assessed using the Korean version of the NPI-Q, which assesses the severity and frequency of 12 items within the preceding 4 weeks [34]. The 12 items of the NPI-Q were classified into three major subdomains (mood, hyperactivity, and psychosis) [35], and total scores were calculated by summing the scores of the 12 items (Method S2).

2.5 | NMS Assessment Based on Questionnaires

The definition of “probable RBD (pRBD)” was based on the RBDSQ [36], adopting a cut-off score of ≥ 6 [37] (Method S3). Other NMSs were assessed with the NMSQ, a 30-item survey covering nine domains [38]. Additionally, the NMSQ below the substantia nigra (NMSQ_{BelowSN}) score is a composite score derived from a subset of 14 NMS items likely to involve a neurological substrate caudal to the substantia nigra [39]. Detailed information is described in Method S3.

2.6 | Acquisition, Processing, and Quantitative Analyses of PET and MR Images

Detailed protocols are described in Methods S4–S5. DAT availability was estimated by using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) and in-house software, implemented in MATLAB R2021a (MathWorks, Natick, MA). The asymmetry index (AI) and anteroposterior (AP) gradient for striatal DAT availability were calculated as described previously (Method S5) [40]. In volumetric analyses of MRI, AssemblyNet software was employed [41].

2.7 | Assessment of the Clinical Measures Related to PD Prognosis

Patients visited our outpatient clinic at 3- to 6-month intervals. At each visit, two movement-disorder specialists (Y.H.S. and P.H.L.) evaluated the emergence of wearing off, dyskinesia, and freezing of gait (FOG) as described in Method S6 [40, 42]. Moreover, PDD conversion was determined by consensus between two neurologists and one neuropsychologist (Method S7) [29, 33, 43].

2.8 | Statistical Analyses

The demographic and clinical characteristics between groups were compared using analysis of variance or the Kruskal–Wallis test for continuous variables, and chi-square or Fisher's exact tests for categorical variables. A linear-by-linear association test was used to examine whether dysautonomia severity increased with the degree of olfactory dysfunction. When comparing autonomic dysfunction severity, cognitive performance, NPS burden, and DAT availability among the three olfactory groups, analyses of covariance (ANCOVA) were performed, using

age, sex, cognitive status, and disease duration as covariates. Multiple comparisons were addressed by using the false discovery rate (FDR) method.

Potential neural substrates of olfactory dysfunction were sought by using partial correlation analyses between the CC-SIT score and imaging variables (regional DAT availability and gray matter volume [GMV]), adjusting for age, sex, cognitive status, and disease duration. Furthermore, path analyses were performed to investigate whether the associations between olfaction (CC-SIT score) and cognitive/neuropsychiatric symptoms were mediated by the identified neural substrates using PROCESS Macro v4.2 [44]. Where multiple structural correlates showed significant associations with both olfactory function and cognition, we selected the region with the lowest Akaike information criterion as the potential mediator.

Cox proportional hazards models (adjusting for age, sex, education, and cognitive status at baseline) were constructed to investigate whether baseline olfactory status exerts an independent effect on the risk of developing motor complications or PDD. In these analyses, only non-demented participants with > 36 months of follow-up ($n = 180$, 69.5%) were included. Additionally, subgroup analyses were repeated for groups based on pRBD and olfactory status (PD patients with both olfactory impairment and pRBD [PD^{OLF+pRBD+}] vs. normosmic PD patients without pRBD [PD^{OLF-pRBD-}]).

Analyses were performed using SPSS (v28.0, IBM Corporation, Armonk, NY) or R software (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria). Results with $p < 0.05$ were considered statistically significant.

3 | Results

3.1 | Demographic and Clinical Characteristics

The demographic and clinical characteristics of patients are summarized in Table 1. Among the 259 included patients, 217 patients exhibited olfactory dysfunction (83.8%), including 55.2% with hyposmia and 28.6% with anosmia. Female sex was significantly more prevalent in the normosmia (64.3%) compared to the hyposmia (39.9%) and anosmia groups (29.7%; $p < 0.001$). The anosmia group was significantly older both at diagnosis and onset compared to the hyposmia or normosmia groups (all $p < 0.001$). Mini-Mental State Examination scores were lower in the anosmia than in the normosmia and hyposmia groups ($p < 0.001$) but were similar between the normosmia and hyposmia groups ($p = 0.068$).

3.2 | Autonomic Function According to Olfactory Function

The CASS total score was significantly negatively correlated with the CC-SIT score (Spearman $\rho = -0.301$, $p < 0.001$), even after adjusting for age, sex, cognitive status, and disease duration (partial $\rho = -0.219$, $p = 0.001$) (Figure 1A).

The severity of dysautonomia tended to increase with olfactory dysfunction in the following order: normosmia, hyposmia,

TABLE 1 | Clinical characteristics according to olfactory status.

	Normosmia N=42	Hyposmia N=143	Anosmia N=74	P
Age at diagnosis, years	67.97 ± 7.31	68.38 ± 9.09	73.75 ± 7.39	<0.001 ^b
Onset age, years	65.92 ± 7.59	66.78 ± 9.16	72.36 ± 7.39	<0.001 ^b
Sex, female, n (%)	27 (64.3)	57 (39.9)	22 (29.7)	<0.001
Disease duration, years	1.92 ± 1.40	1.60 ± 1.41	1.39 ± 1.18	0.120
Education, years	9.93 ± 3.80	10.34 ± 4.69	10.63 ± 4.84	0.732
MMSE score	27.64 ± 1.94	26.66 ± 2.81	25.20 ± 3.95	<0.001 ^b
UPDRS Part III	20.07 ± 8.73	23.04 ± 8.30	23.54 ± 8.34	0.079
Motor phenotype				0.265
Tremor, n (%)	17 (40.5)	37 (25.9)	17 (23.0)	
Indeterminate, n (%)	7 (16.7)	21 (14.7)	13 (17.6)	
PIGD, n (%)	18 (42.9)	85 (59.4)	44 (59.5)	
Cognitive status				0.657
Intact cognition, n (%)	18 (42.9)	48 (33.6)	24 (32.4)	
MCI, n (%)	23 (54.8)	84 (58.7)	44 (59.5)	
Dementia, n (%)	1 (2.4)	11 (7.7)	6 (8.1)	
Presence of RBD, n (%)	11 (26.2)	53 (37.1)	42 (56.8)	0.002
Pattern of DAT loss ^a				
Asymmetry index	8.40 ± 6.91	8.77 ± 7.13	6.51 ± 4.98	0.053
Anteroposterior gradient	1.24 ± 0.25	1.23 ± 0.19	1.16 ± 0.17	0.072
Vascular risk factors				
Hypertension, n (%)	19 (45.2)	63 (44.1)	43 (58.1)	0.135
Diabetes, n (%)	11 (26.2)	31 (21.7)	17 (23.0)	0.843
Dyslipidemia, n (%)	18 (42.9)	50 (35.0)	31 (41.9)	0.491

Abbreviations: DAT = dopamine transporter; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PI GD = postural instability and gait difficulty; RBD = rapid eye movement sleep behavior disorder.

^aAnalyses of covariance were performed for comparison using age, sex, cognitive status, and disease duration as covariates.

^bSignificant difference between anosmia and the other groups in post hoc analysis.

anosmia ($p^{\text{trend}} < 0.001$) (Figure 1B). The anosmia group revealed higher CASS total scores (4.81 ± 2.28), compared to the normosmia (2.45 ± 2.42 ; $p = 0.003$) and hyposmia (3.66 ± 2.45 ; $p = 0.011$) groups, but was similar in the hyposmia and anosmia groups. Adrenergic dysfunction was also more pronounced in the anosmia (2.27 ± 1.16 ; $p = 0.001$) and hyposmia groups (1.78 ± 1.36 ; $p = 0.005$) than in the normosmia group (1.12 ± 1.27) (Table 2).

3.3 | Cognitive/Neuropsychiatric Symptoms According to Olfactory Function

ANCOVA results comparing cognition and NPS burden across olfactory groups are presented in Table 3, with post hoc analyses in Table S1. The anosmia group exhibited worse global cognitive composite scores than the normosmia and hyposmia groups (both $p < 0.001$), while the normosmia and hyposmia groups

had similar scores ($p = 0.145$). Domain-specific analyses showed that the anosmia group had worse performance in the memory (anosmia -0.58 ± 0.08 vs. normosmia -0.17 ± 0.10 , $p = 0.001$; hyposmia -0.36 ± 0.05 , $p = 0.019$) and frontal/executive scores (anosmia -0.69 ± 0.09 vs. normosmia -0.31 ± 0.13 , $p = 0.016$; hyposmia -0.39 ± 0.07 , $p = 0.010$), whereas normosmia and hyposmia were comparable.

The NPI-Q total scores and mood subdomain scores differed significantly across olfactory groups, with increasing severity from normosmia to anosmia. Post hoc analyses revealed significant differences in NPI-Q total scores between all olfactory group pairs, with higher scores in the anosmia group (7.66 ± 0.81) than in the hyposmia group (4.67 ± 0.57 ; $p = 0.003$) and normosmia group (1.43 ± 1.06 ; $p < 0.001$), and in the hyposmia group than in the normosmia group ($p = 0.007$). The mood subdomain exhibited a similar pattern, with significant differences between all olfactory group pairs (Table S1).

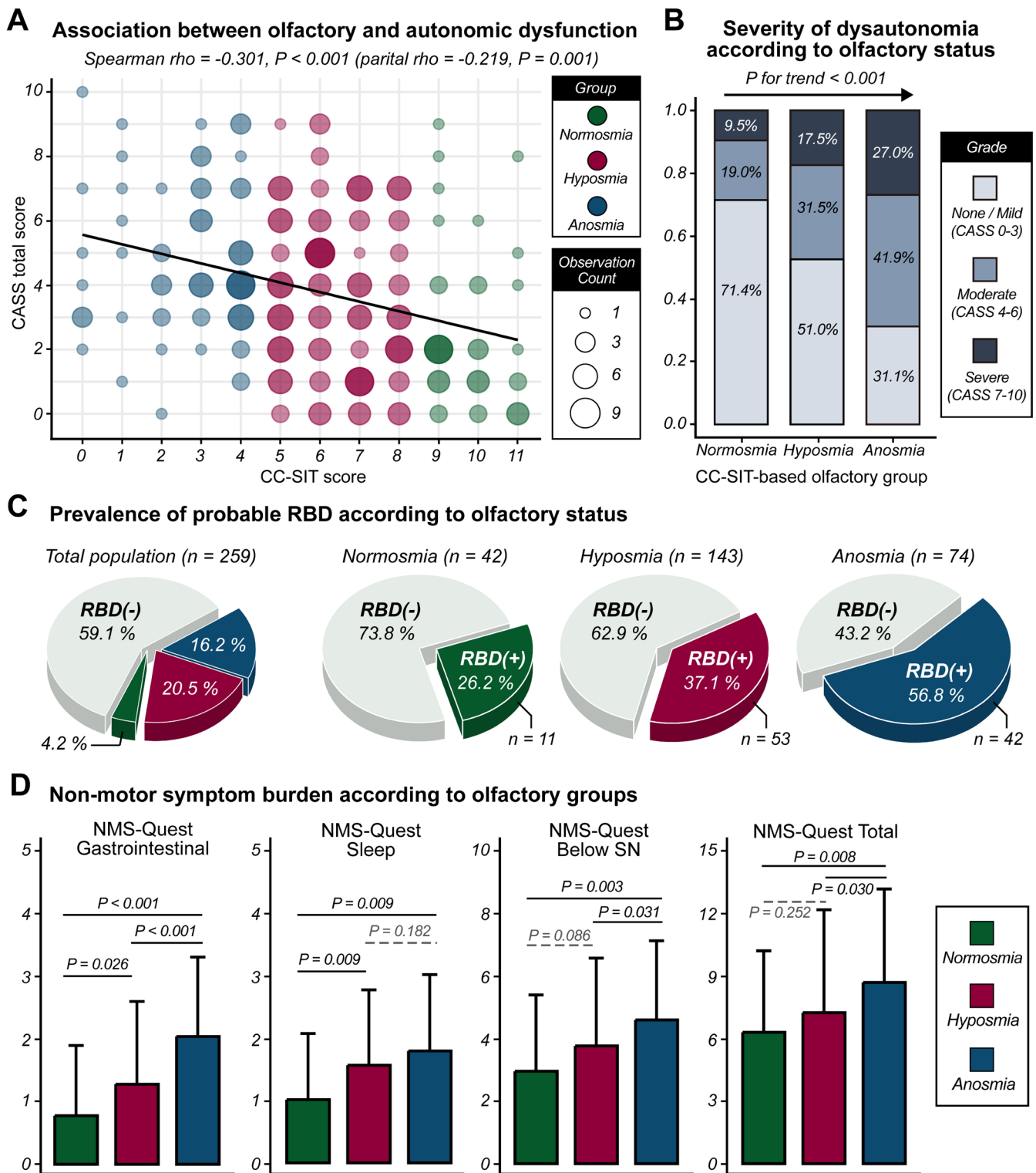


FIGURE 1 | Non-motor symptom profiles according to olfactory dysfunction. (A) The Cross-Cultural Smell Identification Test (CC-SIT) score shows a significant negative correlation with the Composite Autonomic Scoring Scale (CASS) total score. (B) The severity of dysautonomia exhibits an increasing trend in accordance with the degree of olfactory dysfunction. (C) The proportion of those who presented with rapid eye movement sleep behavior disorder (RBD) at diagnosis increased in accordance with the severity of olfactory dysfunction. (D) In the Non-Motor Symptom Questionnaire (NMSQ), significant differences were observed in gastrointestinal and sleep disturbance subscores, composite scores below the level of the substantia nigra (SN), and total scores across the olfactory groups.

TABLE 2 | Severity of dysautonomia according to olfactory status.

	Normosmia <i>n</i> = 42	Hyposmia <i>n</i> = 143	Anosmia <i>n</i> = 74	Adjusted <i>p</i>
CASS				
Total score	2.45 ± 2.42	3.66 ± 2.45	4.81 ± 2.28	0.006 ^a
Sudomotor index	0.55 ± 0.97	0.90 ± 1.13	1.19 ± 1.15	0.229
Cardiovagal index	0.88 ± 0.92	0.98 ± 0.95	1.35 ± 1.10	0.452
Adrenergic index	1.02 ± 1.20	1.78 ± 1.36	2.27 ± 1.16	0.005 ^a
Severity of dysautonomia ^b				0.001
None/mild, <i>n</i> (%)	30 (71.4)	73 (51.0)	23 (31.1)	
Moderate, <i>n</i> (%)	8 (19.0)	45 (31.5)	31 (41.9)	
Severe, <i>n</i> (%)	4 (9.5)	25 (17.5)	20 (27.0)	

Note: *p* values corrected for multiple comparisons using the false discovery rate method.

Abbreviation: CASS = Composite Autonomic Severity Scale.

^aPost hoc analysis: Normosmia = Hyposmia < Anosmia.

^bBased on the CASS total score, the severity of autonomic dysfunction was classified as none/mild (CASS 0–3), moderate (CASS 4–6), and severe (CASS 7–10).

TABLE 3 | Cognitive/neuropsychiatric symptom burden according to olfactory status.

	Normosmia <i>n</i> = 42	Hyposmia <i>n</i> = 143	Anosmia <i>n</i> = 74	Adjusted <i>p</i>
Cognitive performance				
Global composite score	0.03 ± 0.05	−0.05 ± 0.02	−0.19 ± 0.04	0.002^a
Domain-specific score				
Attention	−0.19 ± 0.11	−0.22 ± 0.06	−0.45 ± 0.08	0.080
Language	0.11 ± 0.16	−0.13 ± 0.08	−0.41 ± 0.12	0.054
Visuospatial	−0.30 ± 0.19	−0.53 ± 0.14	−0.76 ± 0.14	0.158
Memory	−0.17 ± 0.10	−0.36 ± 0.05	−0.58 ± 0.08	0.012^a
Frontal/executive	−0.31 ± 0.13	−0.39 ± 0.07	−0.69 ± 0.09	0.032^a
Neuropsychiatric symptom				
NPI-Q total score	1.43 ± 1.06	4.67 ± 0.57	7.66 ± 0.81	<0.001^b
Subdomain score				
Mood	1.25 ± 0.91	3.99 ± 0.48	6.77 ± 0.69	<0.001^b
Hyperactivity	0.13 ± 0.22	0.39 ± 0.15	0.62 ± 0.17	0.261
Psychosis	0.08 ± 0.17	0.22 ± 0.09	0.27 ± 0.13	0.673

Note: Values are presented as adjusted means and standard errors. Analyses of covariance were performed, using age, sex, cognitive status, and disease duration as covariates. *p* values were corrected for multiple comparisons using the false discovery rate method.

^aPost hoc analyses: Anosmia < Hyposmia = Normosmia.

^bPost hoc analyses: Anosmia > Hyposmia > Normosmia.

3.4 | NMS Burden Based on Questionnaires

Based on the RBDSQ, 106 patients (40.9%) had pRBD at diagnosis. The proportion of patients with pRBD increased as olfactory performance worsened (normosmia: 26.2%, hyposmia: 37.1%, and anosmia: 56.8%; $p^{\text{trend}} = 0.001$) (Figure 1C).

Total NMSQ scores were higher in the anosmia (8.93 ± 4.57) than in the hyposmia (7.14 ± 4.82 , $p = 0.007$) and normosmia groups (5.93 ± 3.53 , $p = 0.001$), although the difference between hyposmia and normosmia groups was not significant ($p = 0.132$). The NMSQ_{BelowSN} score increased with the severity

of olfactory dysfunction, from normosmia (2.69 ± 2.19) to hyposmia (3.73 ± 2.76) and anosmia (4.74 ± 2.60) (Figure 1D). NMSQ scores in the gastrointestinal, cardiovascular and sleep-related symptoms showed significant differences across olfactory groups (Table S2).

3.5 | Neural Substrates of Olfactory Dysfunction

DAT availability in the caudate nucleus decreased with worsening olfactory function, with significant inter-group differences (normosmia vs. hyposmia, $p = 0.016$; normosmia vs.

anosmia, $p < 0.001$; hyposmia vs. anosmia, $p = 0.011$), thus exhibiting DAT availability in an olfactory status-dependent manner. Additionally, putaminal DAT availability was higher in the normosmia group than in the hyposmia ($p = 0.004$) and anosmia groups ($p < 0.001$), while the difference between the hyposmia and anosmia groups did not reach statistical significance ($p = 0.103$) (Figure 2A). Caudate DAT availability was significantly associated with the CC-SIT score ($\rho = 0.267$, $p < 0.001$). When investigating the association between olfaction and the pattern of DAT loss, the anosmia group tended to have a lower AI ($p = 0.053$) and AP gradient ($p = 0.072$) than the hyposmia and normosmia groups, with a tendency for correlation of the CC-SIT scores with the AI ($\rho = 0.117$, $p = 0.060$).

CC-SIT scores were significantly associated with bilateral insula, anterior cingulate cortex, and middle temporal gyrus atrophy. Among subcortical structures, CC-SIT scores were significantly associated with reduced GMV in the bilateral

amygdala, hippocampus, thalamus, right nucleus accumbens, and right pallidum. Cortical/subcortical regions showing significant correlation with CC-SIT scores are presented in Figure 2B.

3.6 | Path Analysis

In the mediation model for global cognition, the effect of olfactory function on cognition was partially mediated by caudate DAT availability and hippocampal volume (Figure 3A). Similarly, the effect of olfaction on memory was completely mediated via caudate DAT availability and hippocampal volume (Figure 3B). In the frontal/executive domain, the olfaction–cognition relationship was fully mediated by caudate DAT availability (Figure 3C). Lastly, the relationship between olfaction and NPS in the mood subdomain was partially mediated by dopaminergic cell loss in the caudate nucleus and amygdala atrophy (Figure 3D).

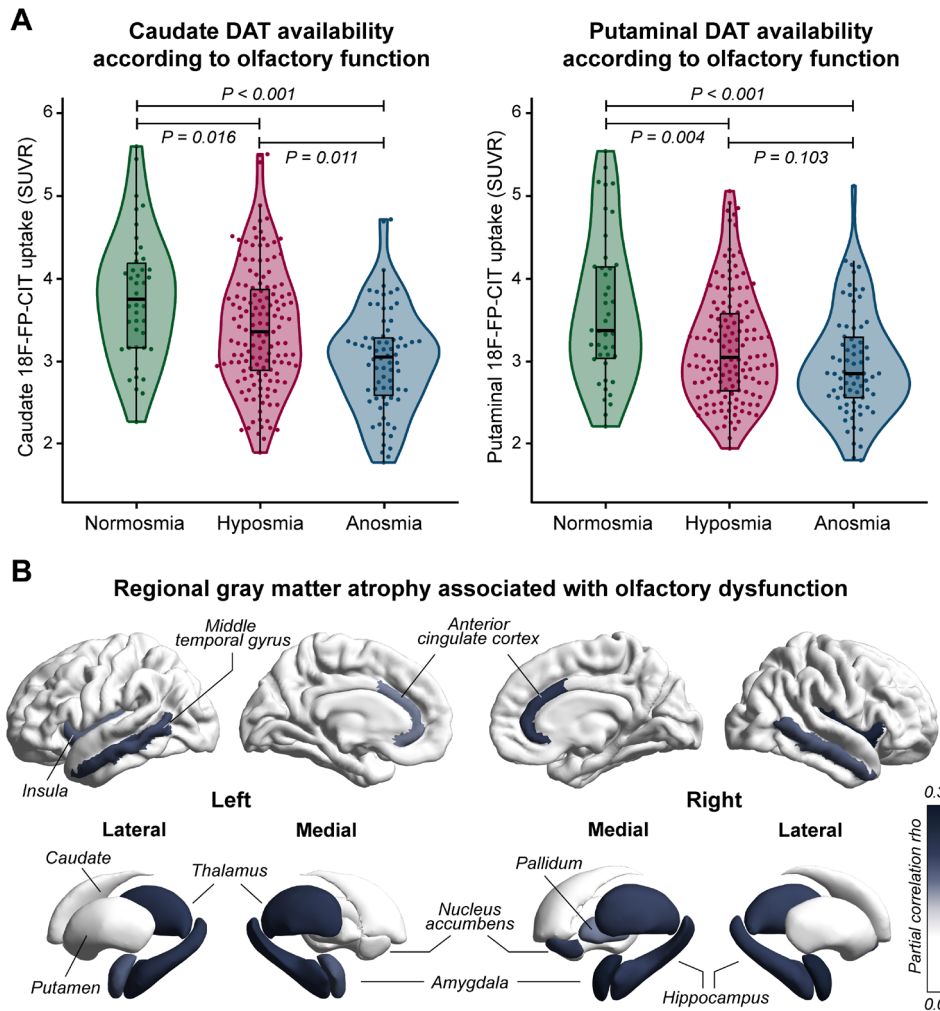


FIGURE 2 | Potential neural correlates of olfactory dysfunction in Parkinson disease. (A) DAT availability in the caudate nucleus decreased with increasing severity of olfactory impairment, while putaminal DAT uptake is relatively preserved in the normosmia group as compared to the hyposmia and anosmia groups. (B) Regional gray matter volume in the bilateral amygdala, hippocampus, thalamus, right nucleus accumbens, and right pallidum revealed significant positive correlations with Cross-Cultural Smell Identification Test scores ($p^{FDR} < 0.05$). Regional atrophy associated with olfactory dysfunction was primarily observed in limbic regions. Abbreviations: DAT = Dopamine transporter; p^{FDR} = false discovery rate-corrected p value; SUVr = standardized uptake ratio.

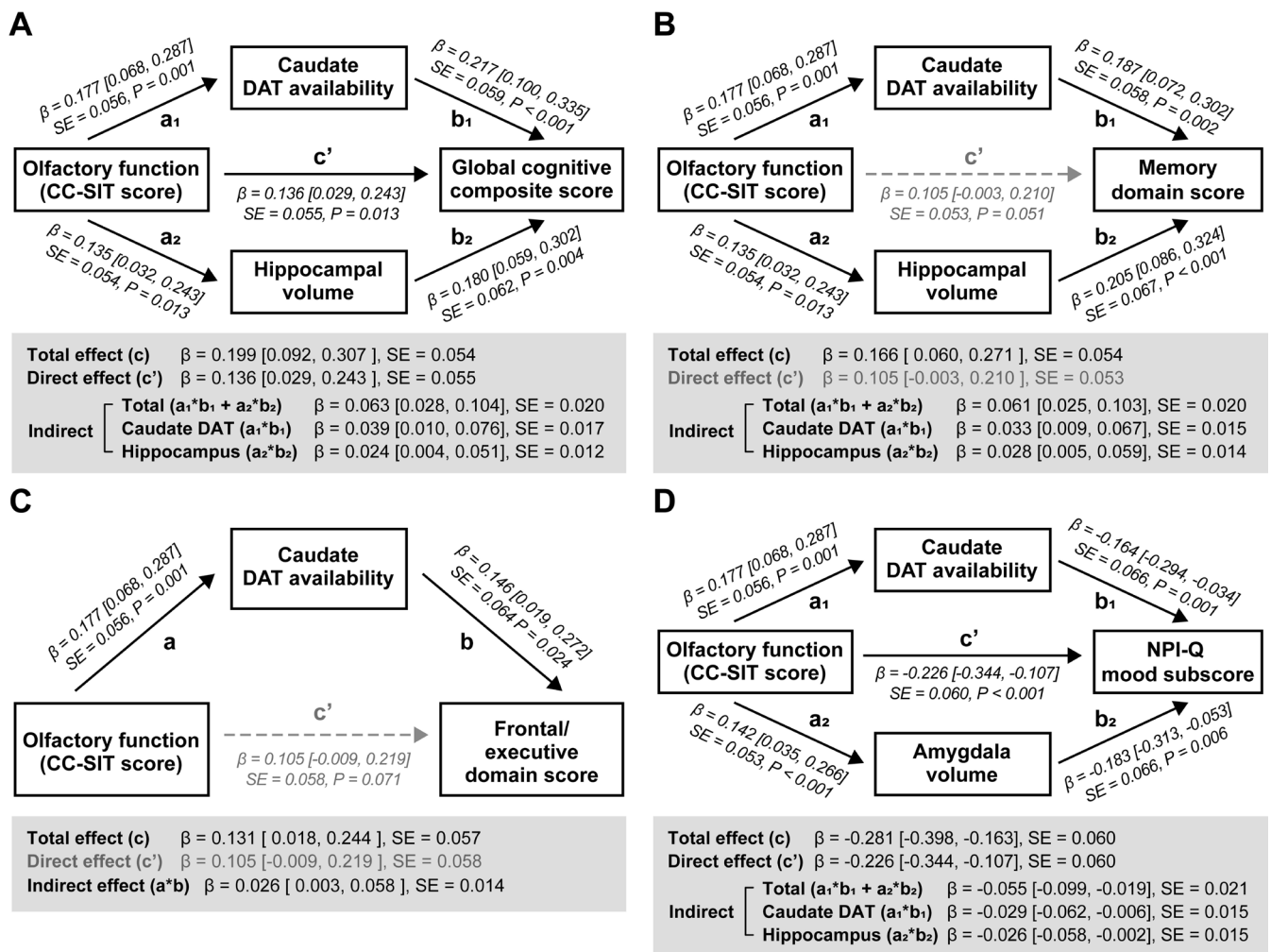


FIGURE 3 | Mediating effect of dopaminergic cell loss and atrophy on the olfaction-cognition relationship. Path analyses demonstrating the mediating effects of caudate dopamine transporter (DAT) availability and hippocampal volume on the olfactory-cognitive relationship. (A, B) The effect of olfactory function on global cognitive score was partially mediated by caudate DAT availability and hippocampal volume (A), while its effect on memory domain was completely mediated by these same factors (B). (C) The effect of olfaction on frontal/executive domain was completely mediated by caudate DAT availability. (D) The association between olfaction and mood was partially mediated by dopaminergic cell loss in the caudate nucleus and amygdala atrophy. Solid lines represent significant paths, while dashed lines represent insignificant paths.

3.7 | Associations of Baseline Olfactory Function With Motor and Cognitive Prognosis

For Cox regression analyses, only participants who were non-demented at baseline and had > 36 months of follow-up ($n = 180$, 69.5%, mean 68.4 ± 28.2 months) were included (37 normosmia, 91 hyposmia, and 52 anosmia). The anosmic group had a significantly increased hazard of developing FOG compared to the normosmic group (HR: 2.571 [95% CI: 1.077–6.134]; $p = 0.033$, Figure 4A). Anosmia was associated with an increased risk of PDD conversion compared to those with hyposmia (HR: 2.783 [95% CI: 1.437–5.390]; $p = 0.002$) or normosmia (HR: 2.579 [95% CI: 1.137–5.851]; $p = 0.023$, Figure 4B). No significant differences were observed in wearing off or dyskinesia development (Figure S1).

In subgroup analyses incorporating pRBD within the olfactory framework, the PD^{OLF+pRBD+} group showed an increased risk of developing FOG (HR: 3.386 [95% CI: 1.182–9.701]; $p = 0.023$)

and PDD (HR: 2.607 [95% CI: 1.101–6.172]; $p = 0.029$, Figure S2) compared to the PD^{OLF-pRBD-} group.

4 | Discussion

Herein, we investigated the clinical manifestations and neural substrates associated with olfactory dysfunction in PD, yielding four major findings. (1) PD patients with greater olfactory dysfunction demonstrated greater NMS burden, characterized by more pronounced cognitive deficits, NPS, and dysautonomia, as well as a higher prevalence of concurrent pRBD, sleep disturbances, and gastrointestinal symptoms at initial diagnosis. This NMS profile agreed with the body-first PD subtype; (2) olfactory deficits were associated with reduced DAT availability in the caudate nucleus and limbic gray matter atrophy; (3) path analyses demonstrated that the olfactory contribution to cognitive and NPS burden was mediated by reduced caudate DAT availability and/or atrophy in limbic regions; and (4) baseline

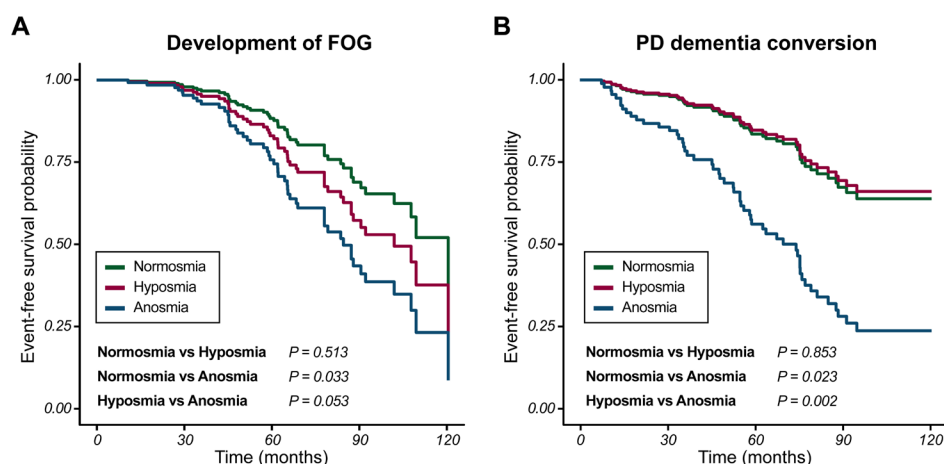


FIGURE 4 | Motor and cognitive outcomes according to baseline olfactory function. Survival curves depicting event-free survival probability for (A) developing freezing of gait (FOG) and (B) dementia conversion in PD patients categorized by baseline olfactory function. In Cox regression analyses, only participants who were non-demented at baseline and had > 36 months of follow-up ($n = 180$) were included. (A) The anosmic group had a significantly increased hazard of developing FOG compared to the normosmic group (HR: 2.571 [95% CI: 1.077–6.134]; $p = 0.033$). (B) PD patients with anosmia demonstrated elevated risk of PDD conversion compared to those with hyposmia (HR: 2.783 [95% CI: 1.437–5.390]; $p = 0.002$) or normosmia (HR: 2.579 [95% CI: 1.137–5.851]; $p = 0.023$). Abbreviations: CI=confidence intervals; FOG=freezing of gait; HR=hazard ratio; PD=Parkinson disease; PDD=Parkinson disease dementia.

olfactory function was associated with divergent clinical trajectories, with anosmic patients showing increased susceptibility to both FOG and PDD conversion. Collectively, olfactory dysfunction serves as a multifaceted clinical marker that captures the convergent degeneration of both nigrostriatal and limbic systems at an early stage, potentially representing a distinct PD phenotype characterized by NMS profiles closely aligning with body-first PD at baseline and unfavorable motor and cognitive outcomes over time.

Evidence increasingly suggests that PD with impaired olfaction tends to exhibit greater NMS burden [6–12], and the associated profiles may partly reflect neural substrates shared with other non-motor manifestations [7, 10–12]. Atrophy or altered networks in the olfactory system [24–27], as well as dopaminergic [15–17], and other neurotransmitters [6, 45] have been proposed as neural underpinnings. In this study, limbic atrophy and reduced caudate DAT uptake were identified as potential neural substrates underlying olfactory impairment in PD, and these substrates played a mediating role in the association of olfactory function with several NMSs. Specifically, our path analyses demonstrated that the associations between olfactory dysfunction and cognitive deficit (frontal/executive and memory domains) were mediated via presynaptic dopaminergic loss and/or limbic atrophy. Similarly, its association with NPSs, particularly the mood subdomain, was partially mediated by dopaminergic denervation and amygdala atrophy. These findings indicate that cognitive/neuropsychiatric symptoms in patients with PD with impaired olfaction may be, at least partly, explained by the dual involvement of dopaminergic and limbic systems. While the shared involvement of common neuroanatomical substrates provides an important framework for understanding the potential link between olfaction and cognitive or neuropsychiatric manifestations, such anatomical overlap alone appears insufficient to fully account for the diverse NMS profiles associated with olfactory dysfunction. Alternatively, the coexistence of olfactory and other NMSs may be explained in

the context of α -synuclein origin site and connectome model, which designates PD phenotypes based on the spreading pattern of synuclein pathology—“brain-first” (central to peripheral) or “body-first” (peripheral to central) subtypes [9, 21–23]. The position of olfactory dysfunction within this framework has been controversial. Notably, earlier investigations had emphasized the involvement of α -synuclein pathology in the olfactory bulb and related structures, thus designating olfactory dysfunction as NMS suggestive of the brain-first subtype [24–26]. However, this perspective was challenged by recent evidence showing that the unilateral involvement characteristic of brain-first PD leaves contralateral olfactory structures intact during early stages, thereby resulting in relatively preserved olfaction compared to that in body-first PD [46]. Our findings help clarify this uncertainty by demonstrating the association of impaired olfaction with pronounced cognitive deficits and NPS, dysautonomia, and higher prevalence of concurrent pRBD and gastrointestinal symptoms—traits resembling the body-first subtype. Notably, olfactory dysfunction is highly prevalent in isolated RBD, a well-established prodromal state of the body-first PD [2, 3], and multimodal imaging studies have shown that PD patients with RBD exhibit more severe olfactory dysfunction than those without [9]. Furthermore, several ^{123}I -Metaiodobenzylguanidine (MIBG) scintigraphy studies have revealed that PD with cardiac sympathetic denervation—another marker of body-first PD—more commonly present with impaired olfaction than those with intact innervation, with MIBG uptake correlating with olfactory performance [8, 47].

Although the perspective of considering olfactory dysfunction as a feature of body-first PD explains many of our findings, it does not readily account for some of our observations. A substantial proportion of PD patients with olfactory impairment did not exhibit significant dysautonomia (hyposmic patients with none/mild dysautonomia: 28.2%; anosmic patients with none/mild dysautonomia: 8.9%) (Table 2) or pRBD (hyposmic patients without pRBD: 62.9%; anosmic patients without pRBD: 43.2%)

(Table 1). This heterogeneity aligns with our recent findings that combined olfactory and autonomic dysfunction, rather than isolated symptoms, defines a distinct subtype with worse motor/cognitive prognosis [10, 12]. Similarly, the PD^{OLF+pRBD+} group demonstrated poorer outcomes than the PD^{OLF-pRBD-} group (Figure S2). These observations underscore that clustering NMS profiles, rather than individual symptoms, may better characterize PD phenotypes.

Our study had some limitations. First, olfactory symptom assessment based on the CC-SIT has inherent limitations in delineating the specific anatomical regions involved in olfactory dysfunction [4, 24–27]. Unlike comprehensive olfactory batteries such as the “Sniffin’ Sticks” [48], which systematically assess odor threshold, discrimination, and identification, the CC-SIT evaluates olfactory function solely through odor identification performance [30]. Since odor identification tasks require higher cognitive processing, including semantic integration [4], cognitive impairment may confound interpretation and overstate the degree of olfactory dysfunction. Furthermore, the CC-SIT includes only 12 items of multiple-choice questions, which may reduce sensitivity for subtle olfactory deficits [30]. Second, while olfaction, dysautonomia, and cognition were evaluated using objective instruments, assessment of other NMS relied primarily on subjective, self-reported questionnaires. For instance, the presence of RBD was determined using the RBDSQ [36], which has modest specificity that can be compromised by obstructive sleep apnea or periodic limb movement disorders [49], thereby providing lower diagnostic accuracy compared to polysomnography. In addition, the NMSQ is a binary (yes/no) screening tool that cannot capture symptom severity or frequency, limiting interpretation of NMS burden [38]. Accordingly, our questionnaire-based results should be interpreted with caution. Third, while all included patients demonstrated sustained levodopa responsiveness and had no atypical features throughout the follow-up, the extent of motor improvement could not be quantified owing to the absence of on-medication UPDRS Part III ratings.

Despite these limitations, the study had several strengths. The principal strength of our study was the well-characterized cohort of treatment-naïve PD. Since NMSs are significantly influenced by anti-Parkinsonian medication, our population was ideal for assessing NMSs in relation to olfactory deficits. Moreover, all participants underwent comprehensive evaluations, including AFT, and neuropsychological examinations, alongside MRI and DAT scans, providing quantitative measures. This multimodal approach significantly improves over previous studies that focused on isolated symptoms, offering a thorough characterization of the relationship between olfactory dysfunction and the broader NMS spectrum.

Overall, olfactory dysfunction in PD extends beyond an isolated NMS. Olfactory dysfunction constitutes an informative clinical marker associated with early neurodegenerative processes involving both nigrostriatal and extra-nigrostriatal (i.e., limbic regions) pathways. Importantly, olfactory impairment, particularly anosmia, may potentially represent a distinct phenotype exhibiting baseline NMS profiles resembling body-first PD and poor motor/cognitive prognosis, providing insights into phenotypic variance in PD.

Author Contributions

Yeeun Sun: conceptualization, writing – original draft, data curation, formal analysis, methodology, visualization. **Han Kyu Na:** conceptualization, data curation, methodology, formal analysis, writing – original draft, writing – review and editing. **So Hoon Yoon:** methodology, data curation. **Quynh Phuong Vo:** data curation, formal analysis. **Chan Wook Park:** data curation, writing – review and editing. **Jung Hyun Lee:** writing – review and editing, data curation. **Yun Young Choi:** data curation, writing – review and editing. **Han Soo Yoo:** data curation, writing – review and editing. **Young H. Sohn:** data curation, writing – review and editing. **Chul Hyoung Lyoo:** data curation, formal analysis. **Phil Hyu Lee:** conceptualization, methodology, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1.** Supplementary Information.