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Hyposmia may predict development of freezing of gait in Parkinson's disease

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Abstract

To explore the effect of olfactory dysfunction on treatment of motor manifestations in Parkinson's disease (PD). The current longitudinal retrospective cohort study consecutively recruited 108 de novo PD patients. Of whom 29 were normosmia and 79 were hyposmia, respectively, which was determined by the Korean Version of Sniffin' Sticks Test II at the time of diagnosis. All the participants underwent serial clinical examinations including Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Examination, and Montreal Cognitive Assessment. The normosmic group demonstrated a significantly greater reduction of the UPDRS III score (30.3 ± 5.9 to 21.9 ± 5.1) than that of the hyposmic group (34.5 ± 9.3 to 28.5 ± 8.1) from baseline to 1-year later (p, 0.003; Bonferroni correction for $p < 0.0045$). Of subdomains in UPDRS III, the axial domain revealed a remarkable decrease in the normosmic group. Further, the hyposmic group exhibited a higher development rate of freezing of gait (FOG) compared to the normosmic group (29/79 (36.7%) vs 2/29 (6.9%); p, 0.002) during 33.9 ± 7.7 months of the mean follow-up period. A Cox proportional hazards model demonstrated the hyposmia to be a significant risk factor for the future development of FOG (HR, 4.23; 95% CI 1.180–17.801; p, 0.05). Our data demonstrated the olfactory dysfunction to be a significant risk factor for the development of the FOG in PD. Hyposmic PD patients should be paid more careful attention to the occurrence of FOG in the clinical practice.

Keywords Parkinson disease · Smell · Gait · Cohort studies

Introduction

Olfactory dysfunction is recognized to be one of the most significant risk factors for the future development of Parkinson's disease (PD). It widely exists, even down to a mild extent, in patients with rapid eye movement sleep behavior disorder, another major prodromal illness of the PD (Miyamoto et al. 2010). A large-scale population-based study demonstrated an olfactory dysfunction to precede the emergence of motor dysfunction in PD at least by 4 years (Ross et al. 2008), which was identified by almost 90% of PD patients at their time of diagnosis (Doty 2012; Doty et al. 1988). Every different type of olfactory examination across the odor detection, identification and discrimination test have revealed consistent results of smell difficulties in the patients with PD (Müller et al. 2002). Lack of olfactory improvement by dopaminergic treatment may suggest the pathologic contribution predominantly by out of the dopaminergic system (Doty 2012). Notwithstanding frequent presentation among patients with Alzheimer's dementia (Velayudhan 2015) or even elderly general population (Murphy et al. 2002), the olfactory function has its own noteworthy capability in differentiating PD from other neurodegenerative disorders (Wenning et al. 1995).

Given the olfactory apparatus as an initial induction site of an alpha-synuclein, the olfactory function may be closely related to the multiple axes of clinical manifestations in PD. Hyposmia was positively correlated with an apathy (Hong et al. 2015) or autonomic dysfunction (Goldstein et al. 2010). Previous literature has described olfactory dysfunction to be a significant predictor for the development of cognitive

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decline and neuropsychiatric manifestations (Baba et al. 2012; Stephenson et al. 2010). As such, a number of non-motor manifestations are coupled with olfactory dysfunction in PD. On the other hand, there also have been multiple studies investigated the relationship between the olfactory dysfunction and motor manifestations in PD (Yoo et al. 2020; Berendse et al. 2011; Doty et al. 1988; Cavaco et al. 2015; Lee et al. 2015). PD patients with normosmia demonstrated less motor severity with benign clinical history than those in hyposmic patients, albeit comparable volume of nigral dopamine (Lee et al. 2015), which has been less consistent so far. In the midst of the conflicting results on impact of the olfaction on motor manifestations in PD, few longitudinal studies have been investigated to date. Hence, we sought to replicate the relationship between olfactory dysfunction and motor manifestations in PD through exploratory investigation out of our longitudinal retrospective cohort registry.

Materials and methods

Study populations

The current retrospective joint cohort study included consecutive patients who had confirmed the diagnosis of PD from respective movement disorder centers affiliated in the Ilsan Paik and Sanggye Paik Hospital. Clinical diagnosis of the PD was established upon the clinical diagnostic criteria of the movement disorder society (Postuma et al. 2015). Participants who had the following clinical conditions were excluded from the study: (1) secondary Parkinsonism, (2) atypical Parkinsonism, (3) structural or functional primary rhinological disorders. All the participants underwent the Korean Version of Sniffin' Sticks Test (KVSS) II, brain magnetic resonance imaging, [^{18}F] *N*-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography scan at their time of PD diagnosis. This study was approved for clinical research and investigation by the Institutional Review Board of Ilsan Paik Hospital, Inje University. (Approval identifier, 2021-01-025).

Korean version of Sniffin' Sticks Test

The KVSS II test was first released in 1999 (Hong et al. 1999) as a modified form of the original Sniffin' Sticks Test which already had been developed in Germany (Kobal et al. 1996). It included a couple of replaced odor items more familiar to the Korean culture and custom and comprised three different sub-tests, an olfactory threshold test (score range 0–16), an odor discrimination test (score range 0–16), and an odor identification test (score range 0–16). Each sub-test presented 16 different items, one point for each correct answer, and a composite Threshold-Discrimination-Identification (TDI) score (range 0–48) was estimated as a final measurement (Hong et al. 1999). This validated test demonstrated considerable test–retest reliability and remarkable correlations with another previously established smell function tests (Cho et al. 2009; Hong et al. 2011). Defined criteria for the TDI score included 0–20 for anosmia, 20.25–27 for hyposmia, and 27.25–48 for normosmia (Hong et al. 1999; Cho et al. 2009). All targeted patients in the current cohort were classified into two subgroups based on the customized TDI score criteria, i.e. a normosmic (27.25–48) and a hyposmic group (0–27), respectively.

Clinical assessment

Clinical examinations including the Unified Parkinson's Disease Rating Scale (UPDRS), the Korean version of the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA) were tested twice, at the time of PD diagnosis and 1 year later, in all participants. UPDRS III, the motor scale, was sub-classified into four sub-domains as follows, rigidity (item 22; range 0–20), bradykinesia (item 23–26, and 31; range 0–36), tremor (item 20 and 21; range 0–28), and axial manifestation (item 18, 19, 27–30, and neck rigidity cited in item 22; range 0–28) (Palmer et al. 2010). The UPDRS was examined in drug naïve "off" state at the baseline and "on" state 1 year later, respectively. Levodopa equivalent dose (LED) which represents the total amount of individually taking dopaminergic medications was calculated according to the previous work (Tomlinson et al. 2010) at 1 year later from the baseline. Every participant had received standard medical treatment for PD which was individually tailored and optimally scheduled. Screening for the absence or presence of the newly developed motor fluctuation, peak dyskinesia, cognitive impairment, and freezing of gait (FOG) was performed at every visit from all patients throughout the whole follow-up period. We used the conventional and well-known definition of the FOG which is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" in the previous literature (Nutt et al. 2011).

Statistical analysis

Data were analyzed retrospectively and longitudinally. To assess the demographic characteristics, an independent *t*-test and χ^2 test were performed to compare group differences for each variable. The normality of the continuous variables was evaluated using the Kolmogorov–Smirnov test. Comparison of group differences in the longitudinal changes of the clinical parameters was analyzed using the linear mixed effects model, which has included the age, time, group and group by time interaction for fixed effects and the subject for random effects, respectively. Multiple linear regression was

employed to examine the relationship between the KVSS score and the 1-year gap of UPDRS motor scores from the baseline with adjusting for the age, sex, disease duration, and baseline UPDRS III score. To maintain a type I error of 0.05, the Bonferroni method for multiplicity correction was employed on sub-categorical analysis of all the variables. Survival analysis including a Cox proportional hazards-regression was employed to investigate the hazard ratio (HR) of the olfactory function on the development of FOG. A two-tailed level of $p < 0.05$ was considered to be significant. All statistical analyses were performed using R (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) and Rex (Version 3.0.3, RexSoft Inc., Seoul, Korea) (RexSoft (2018). Rex: Excel-based statistical analysis software. URL http://rexsoft.org/).

Table 1 Baseline demographics of targeted participants with de novo Parkinson's disease

	Normosmia ($n=29$)	Hyposmia ($n=79$)	p
Age, year	58.9 ± 10.6	66.2 ± 9.1	< 0.001
Men, *n* (%)	19 (65.5)	43 (54.4)	0.705
Age of onset, year	57.7 ± 10.6	65.1 ± 9.2	< 0.001
Disease duration, year	1.2 ± 1.0	1.1 ± 0.7	0.583
Education, year	10.0 ± 5.3	9.0 ± 5.1	0.365
KVSS II, TDI score	32.8 ± 3.3	17.4 ± 6.6	< 0.001
Odor threshold test	15.9 ± 0.4	9.5 ± 4.8	< 0.001*
Odor discrimination test	8.7 ± 2.7	4.1 ± 1.7	< 0.001*
Odor identification test	8.2 ± 1.8	3.9 ± 1.9	< 0.001*

KVSS Korean version of the Sniffin' stick, *TDI* threshold-discrimination-identification

*Significance with Bonferroni multiple correction ($p < 0.0167$)

Results

Demographic characteristics

We identified a total of 108 de novo PD patients, of whom 29 were normosmic and 79 were hyposmic, respectively. The diagnostic confidence has demonstrated 95/108 (88.0%) patients for clinically established PD [normosmic group, 26/29 (89.7%); hyposmic group, 69/79 (87.3%)] and 13/108 (12.0%) for clinically-probable PD [normosmic group, 3/29 (10.3%); hyposmic group, 10/79 (12.7%)], respectively, without group differences. All the participants' mean follow-up duration was 33.9 ± 7.7 months (median 36; min–max 14–45). Clinical data and demographic characteristics are summarized in Table 1. The hyposmic group was older than the normosmic group, but there was no significant group difference in length of the disease duration. The hyposmic group showed lower performance across every sub-test of the KVSS II compared to the normosmic group. We did not find any patients with cognitive decline amounting to dementia at the time of PD diagnosis from all study populations.

Comparative analysis for longitudinal changes of clinical parameters of Parkinson's disease

Each of the clinical parameters including the UPDRS I–IV, MMSE and MoCA did not demonstrate any between-group differences at the baseline. However, the patients whose baseline UPDRS III score was higher than 75th percentile among each group revealed significantly higher UPDRS III score in the hyposmic group ($n=21/79$; 46.5 ± 5.0) than that of the normosmic group ($n=8/29$; 37.4 ± 2.3; $p < 0.001$).

The total UPDRS score of the normosmic group was markedly reduced (baseline to 1-year later, 40.7 ± 9.8 to 30.4 ± 8.4) than the hyposmic group (45.9 ± 12.2 to 39.1 ± 9.6). In the UPDRS I and II, however, longitudinal changes of the respective score did not differ between the two groups (Table 2). Meanwhile, the normosmic group showed a significantly greater decline of the UPDRS III score (normosmic vs hyposmic group; gap, − 8.4 ± 5.6 vs − 6.0 ± 2.7; group by time interaction, $p=0.003$), of which the axial symptoms demonstrated a remarkable decline in particular (gap; − 3.8 ± 2.5 vs − 1.5 ± 1.3; $p < 0.001$) with controlling for a covariate of the age. (Supplementary Fig. 1) Reversely, longitudinal alterations of the axial manifestations did not differ depending on the different level of the age after controlling the smell group as a covariate (age by time interaction, $p=0.645$). Changes of the MMSE and MoCA scores were not evident over time between the groups.

During the whole study participation, the motor fluctuation [normosmic vs hyposmic group; 7/29 (24.1%) vs 21/79 (26.6%); *p*, 0.797] and the peak dyskinesia [2/29 (6.9%) vs 11/79 (13.9%); *p*, 0.507] were developed in each group, which did not show any notable group differences in prevalence and in time of the symptom onset (months after initiation of the PD medication; motor fluctuation, 33.4 ± 5.1 vs 30.3 ± 6.6; peak dyskinesia 31.0 ± 4.2 vs 33.7 ± 3.6), respectively. One out of 29 (3.4%) normosmic and six out of 79 (7.6%) hyposmic patients were newly diagnosed with dementia during the follow-up period (*p*, 0.639).

Contribution of smell dysfunction on motor function and development of freezing of gait

In the multiple linear regression analysis presenting the smell function for the motor functions in the Table 3, the increasing KVSS score was significantly associated with the increasing gap of the UPDRS III and its axial sub-score, respectively, from baseline to 1 year later, albeit controlling the effect of the age, sex, disease duration, and baseline

Table 2 Longitudinally altered profile of the motor manifestations in patients with Parkinson's disease

	Normosmia ($n=29$)		Slope (SE)	Hyposmia ($n=79$)		Slope (SE)	p*
	Baseline	1-year later		Baseline	1-year later		
UPDRS I	1.8 ± 1.8	2.4 ± 1.8	0.58 ± 0.41	2.4 ± 1.9	2.7 ± 2.1	0.34 ± 0.25	0.615
UPDRS II	8.6 ± 6.4	6.1 ± 4.2	− 2.48 ± 0.78	8.9 ± 5.8	7.8 ± 3.6	− 0.13 ± 0.46	0.129
UPDRS III	30.3 ± 5.9	21.9 ± 5.1	− 8.41 ± 1.04	34.5 ± 9.3	28.5 ± 8.1	− 6.01 ± 3.00	0.003
Tremor	3.4 ± 1.7	2.9 ± 1.6	− 0.99 ± 0.10	4.2 ± 1.9	3.2 ± 1.6	− 0.52 ± 0.18	0.022
Rigidity	6.0 ± 1.7	3.7 ± 1.7	− 2.31 ± 0.21	7.3 ± 2.2	5.5 ± 1.9	− 1.80 ± 0.17	0.094
Bradykinesia	12.1 ± 3.3	10.2 ± 4.6	− 1.83 ± 0.93	13.7 ± 6.3	11.9 ± 5.8	− 1.75 ± 0.34	0.919
Axial symptoms	8.8 ± 2.7	5.0 ± 1.9	− 3.76 ± 0.47	9.4 ± 2.3	7.9 ± 2.2	− 1.47 ± 0.14	< 0.001
UPDRS IV		1.7 ± 1.0			2.0 ± 1.9		0.413
LED		377.5 ± 131.9			415.0 ± 102.2		0.122
MMSE	25.5 ± 3.5	24.4 ± 4.2	− 1.10 ± 0.29	24.5 ± 3.7	23.1 ± 4.1	− 1.39 ± 0.18	0.408
MoCA	20.9 ± 4.0	18.6 ± 4.2	− 1.86 ± 0.28	19.1 ± 4.2	17.9 ± 4.8	− 1.62 ± 0.18	0.487

UPDRS Unified Parkinson's Disease Rating Scale, *LED* levodopa equivalent dose, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment

*Group by time interaction with adjustment for the age. Significance with Bonferroni multiple correction ($p < 0.0045$, 0.05/11)

Table 3 Effective predictor of smell function on longitudinal alterations of the motor scale in Parkinson's disease

Gap of motor scale	Predictor	β (SE)	95% confidence interval	p*
UPDRS III				
	KVSS score	− 0.23 (0.05)	− 0.327 to − 0.139	< 0.001
	Age	− 0.09 (0.05)	− 0.179 to − 0.006	0.066
Tremor				
	KVSS score	0.03 (0.01)	0.003–0.058	0.032
	Age	0.02 (0.01)	− 0.012 to 0.043	0.263
Rigidity				
	KVSS score	− 0.02 (0.02)	− 0.059 to 0.023	0.387
	Age	0.01 (0.02)	− 0.029 to 0.051	0.591
Bradykinesia				
	KVSS score	− 0.09 (0.05)	0.191–0.009	0.075
	Age	− 0.03 (0.05)	− 0.128 to 0.069	0.551
Axial symptoms				
	KVSS score	− 0.15 (0.03)	− 0.204 to − 0.104	< 0.001
	Age	− 0.08 (0.02)	− 0.133 to − 0.034	0.001

Adjusted covariates include age, sex, disease duration, and motor scale of the Unified Parkinson's Disease Rating Scale

KVSS Korean version of the Sniffin' stick

*Significance with Bonferroni multiple correction ($p < 0.01$, 0.05/5) for sub-categorical analysis of UPDRS III

UPDRS III score. These suggest the higher KVSS score to be related to the better longitudinal improvements of the UPDRS III and its axial motor manifestations, which are in line with the results out of the Table 2.

The hyposmic group demonstrated a markedly higher development rate of the FOG compared to the normosmic group [29/79 (36.7%) vs 2/29 (6.9%); p, 0.002] during the whole follow-up period. The Kaplan–Meier curve with log-rank test demonstrated the significant group difference in the Fig. 1. Time to occurrence of the FOG in the hyposmic group (months; mean ± SD, 34.1 ± 7.2; min–max, 20–45) did not differ from that in the normosmic group (mean ± SD, 35.0 ± 1.4; min–max, 34–36). A subset of patients (n; normosmic group, 6; hyposmic group, 12) has underwent the "Freezing of Gait Questionnaire" (Giladi et al. 2000), which did not demonstrate any between-group differences in the frequency, duration, and severity of FOG (Supplementary Table 1).

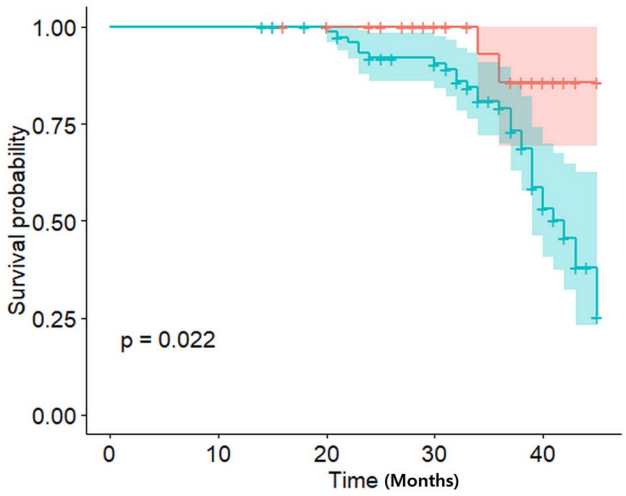

Fig. 1 Estimated Kaplan–Meier curve for the time to the development of freezing of gait in de novo patients with Parkinson's disease

Univariate analysis of the Cox proportional hazards-regression model demonstrated that the hyposmia strongly predicts future development of the FOG [HR, 4.59; 95% confidence interval (CI) 1.087–18.829; *p*, 0.04] in the patients with PD (Table 4). Furthermore, the hyposmia consistently remained as a significant risk factor for the FOG development with controlling for the age, sex, disease duration, and a baseline motor score of the UPDRS (HR, 4.23; 95% CI 1.180–17.801; *p*, 0.05).

Discussion

In the present institution-based retrospective cohort study, we investigated an impact of the smell dysfunction on longitudinal alterations of the clinical manifestations in patients with de novo PD. Upon standard treatment of the PD, the normosmic group demonstrated better response in the treatment of motor manifestations, particularly in the axial manifestations, than the hyposmic group. The hyposmic group had more frequently encountered a FOG in their clinical progress. Furthermore, the hyposmia was demonstrated to be a strong risk factor for the occurrence of the future FOG in the patients with PD. Nonetheless, there might be a caveat in the interpretation of the outcomes of the current investigation because of the potential confounding effect by the older age and potentially malignant PD patients of the hyposmic group. However, we believe that the principal outcomes of the current study including (1) all the outcomes controlling for the age, (2) no between-group differences at the baseline UPDRS and the clinical milestones, such as a cognitive decline or a long-term complication of PD, throughout the follow-up time, and (3) a relatively short follow-up period (mean 33.9 ± 7.7 months) would underpin the outplaying role of the smell dysfunction on the motor manifestations in PD.

In light of bottom–up progression of the Lewy body accumulation from either brain stem or olfactory pathway in PD (Braak et al. 2003), someone could raise an idea like the intimate relationship between the olfactory dysfunction and motor manifestations. A few clinical studies have demonstrated conflicting results (Yoo et al. 2020; Berendse et al. 2011; Doty et al. 1988; Cavaco et al. 2015; Lee et al. 2015), although a majority of them included heterogeneous stage of study populations such that up to 5 years of disease duration. In the two large-scale studies (Yoo et al. 2020; Lee et al. 2015) where investigated such a relationship in the de novo patients with PD, the outcomes were also contrasting and showed a limited level of confidence in the causal relationship because of their cross-sectional methodology. Given the potential floor effect lay between the olfactory dysfunction and motor impairment as alpha-synuclein relentlessly accumulates along the major anatomical substrates, involving the advanced stage of PD participants might render a true association very elusive in the clinical study. Alternatively, a less progressive feature of the smell impairment throughout the natural history of PD (Doty et al. 1992) could be another explanation for the unclear relationship between the

Table 4 Cox Proportional-Hazards Model for prediction of the freezing of gait in Parkinson's disease

Model 1	Crude		
	Hazard ratio	95% Confidence interval	*p*
Normosmic group	Reference		
Hyposmic group	4.59	1.087–18.829	0.04
Model 2	Adjusted*		
	Hazard ratio	95% Confidence interval	*p*
Normosmic group	Reference		
Hyposmic group	4.23	1.180–17.801	0.05

*Adjusted covariates include age, sex, disease duration, and motor scale of the Unified Parkinson's Disease Rating Scale

olfaction and motor severity in the PD. Olfactory epithelium, which is playing a role as a stem or progenitor cell, has a highly active regeneration capacity, where globose and horizontal basal cell restores cellular injury and maintain the biologic integrity (Child et al. 2018). An experimental study in mice demonstrated that dopaminergic interneurons on the glomerular layer of the olfactory epithelium which was treated by 6-hydroxydopamine showed restoration of dopaminergic neurons and further amelioration of olfactory sensory processing in 2 months (Lazarini et al. 2014). Otherwise, different smell tests with different odorants and heterogeneous character of the study population in the previous studies from one another may contribute to the inconsistent results between the olfaction and motor impairment. The current study demonstrated the negative impact of olfactory dysfunction on the treatment of motor manifestations from longitudinal data of the de novo PD patients. However, there needs some compromise for interpretation owing to the follow-up UPDRS motor scale which was examined at drug-on state, instead of off.

Specific contribution of the olfactory dysfunction to the motor treatment in PD is yet to be elucidated. Nonetheless, precedent neuropathologic evidence has posed the putative link between the olfactory and the nigrostriatal dopaminergic system. The advent of Lewy bodies in the olfactory bulb extensively spread through the entire limbic structures including an anterior olfactory nucleus, piriform cortex, amygdaloid complex, entorhinal cortex, and hippocampal formation via cell-to-cell transmission already early in the disease stage and best predicts presence of identical pathology in rest of the brain region (Huisman et al. 2004). Alpha-synuclein density or neuronal loss in the olfactory bulb was correlated with disease duration (Pearce et al. 1995) and UPDRS motor scores, and further accurately distinguished PD from the healthy population (Doty et al. 1988). A decline of olfactory function predicted volume loss across the entire basal ganglia region in patients with PD (Campabadal et al. 2017). Pathological progress of the olfactory pathway pursues toward ventral striatum through the limbic substrate including amygdala and entorhinal region at the stage 3 of Braak, meanwhile, another caudo-rostral extension departing from the brainstem bifurcates into either substantia nigra and basolateral subnuclei of the amygdala in where reciprocally connected to the locus coeruleus and pedunculopontine nucleus (PPN) (Del Tredici and Braak 2016).Conceivable rendezvous of synuclein accumulations from two respective pathway might result in a close linkage between the olfactory and nigrostriatal dopaminergic pathway in the PD (Hawkes et al. 2007).

Olfactory dysfunction was closely associated with axial manifestations and potentially predicted the future development of the FOG in our study. With this regard, a clinical overlap between the olfactory dysfunction and FOG could be elucidated by their respective association with the cognitive dysfunction in common. The previous studies have reported cognitive dysfunction particularly in both the attention (Spildooren et al. 2010) and the frontal execution (Amboni et al. 2008), such as a dual-tasking and set-shifting function, in PD patients with FOG. A multitude of structural and functional neuroimaging researches have revealed diminished cortical volume and cellular activity in the multiple brain regions, especially in the frontal lobe including a supplementary motor area (Fasano et al. 2015). The olfactory dysfunction, as a well-known risk factor for the cognitive impairment in PD (Yoo et al. 2020; Roberts et al. 2016), was also closely implicated to the performance deteriorated in both the attention (Wilson et al. 2006) and the frontal execution (Fagundo et al. 2015; Herman et al. 2018). Affecting the basal forebrain, in particular (Arendt et al. 1983), a pivot of the cholinergic system, might be responsible for the links from one another among the smell, cognition, and further FOG in PD. Therefore, we can speculate the frontal cognitive dysfunction as a putative co-mechanism of the action between the olfactory dysfunction and FOG. However, as not all PD patients with dysfunction in attention or frontal execution showed FOG, further refinement is required.

A progression of the olfactory pathway is coupled with a couple of major anatomical correlates of the gait control in PD. The olfactory trajectory out of the bulb area has an indirect connection with the PPN, a key substrate of the midbrain locomotor region, through the central and basolateral subnuclei of the amygdala (Braak et al. 1994). Mitral cells in the raphe nucleus, the core site of the serotonergic system playing a critical role in ignition and maintenance of the locomotion (Jordan et al. 2008), exhibited a direct connection with the olfactory bulb (Petzold et al. 2009), which was not observed in atypical parkinsonian disorder including progressive supranuclear palsy and multiple system atrophy (Kovacs et al. 2003). The direct relationship between the olfactory system and the MLR has been evidenced by the multiple animal studies. Odor-guided swift behaviors in animals are essential for their survival, such as avoiding predators and searching for food around. For instance, rats run away immediately as they once recognized the cat's odor. They seek for a smell of something to eat all the time to feed themselves. An olfactory system of the lamprey brain directed toward the cuneiform nucleus of the MLR is closely implicated with the immediate defensive mechanism (Derjean et al. 2010). They receive olfactory input via the olfactory tubercle, which in turn directs to the MLR through the lateral hypothalamus, and consequently enables appetite-reactive body movement (Kim et al. 2017). Although being remained largely unknown in humans, given the presence of the analogous response to those in animals, a possible connection between the olfactory system and the locomotor region in humans might be an alternative elucidation for the

potential role of an olfactory dysfunction on occurrence of the FOG in PD.

All the recruited individuals were drug naïve de novo patients with PD, thus the outcomes of the present study indicate the relatively pure pathogenic status of the illness. However, a sampling patient with early-stage alone might contain a slight risk of including heterogeneous patients with potential atypical parkinsonian disorders. The nature of the current retrospective cohort study provides limited evidence of the cause-and-effect relationship between olfactory dysfunction and the FOG in PD. We have examined scores of the second UPDRS III at drug-on status, instead of drug-off, which prevented us to establish the direct detrimental effect of the olfactory dysfunction on motor progression in the study population. The effect from unmeasured confounders of the FOG may potentially exist in the present study. Assessment of the FOG profile in the small subset of patients at fairly early stage of the FOG occurrence might be responsible for the non-significant difference between groups.

Despite the limitations, our data have demonstrated the olfactory dysfunction as a potential risk factor for future development of the FOG in PD. The early-stage PD patients with hyposmia should be paid more attention on the occurrence of FOG throughout the standard treatment in the clinical practice. A prospective larger-scale cohort study with longitudinal clinical parameters would be warranted to best clarify the relationship between olfactory dysfunction and FOG in PD.

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Authors' contributions LJJ designed and conducted the study, analyzed clinical data, interpreted data, and drafted the manuscript. HJY collected and analyzed clinical data. BJS designed and conducted the study, interpreted data, drafted the manuscript, and supervised the study.

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Availability of data and material All the data are open to access to those who applied for and approved by the primary author of the current study.

Declarations

Conflict of interest All of the authors report no disclosures relevant to the manuscript.

References

Amboni M, Cozzolino A, Longo K, Picillo M, Barone P (2008) Freezing of gait and executive functions in patients with Parkinson's disease. Mov Disord 23(3):395–400. https://doi.org/10.1002/mds.21850

Arendt T, Bigl V, Arendt A, Tennstedt A (1983) Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's Disease. Acta Neuropathol 61(2):101–108. https://doi.org/10.1007/bf00697388

Baba T, Kikuchi A, Hirayama K, Nishio Y, Hosokai Y, Kanno S, Hasegawa T, Sugeno N, Konno M, Suzuki K, Takahashi S, Fukuda H, Aoki M, Itoyama Y, Mori E, Takeda A (2012) Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. Brain 135(Pt 1):161–169. https://doi.org/10.1093/brain/awr321

Berendse HW, Roos DS, Raijmakers P, Doty RL (2011) Motor and non-motor correlates of olfactory dysfunction in Parkinson's disease. J Neurol Sci 310(1–2):21–24. https://doi.org/10.1016/j.jns.2011.06.020

Braak H, Braak E, Yilmazer D, de Vos RA, Jansen EN, Bohl J, Jellinger K (1994) Amygdala pathology in Parkinson's disease. Acta Neuropathol 88(6):493–500. https://doi.org/10.1007/bf00296485

Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24(2):197–211. https://doi.org/10.1016/s0197-4580(02)00065-9

Campabadal A, Uribe C, Segura B, Baggio HC, Abos A, Garcia-Diaz AI, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Junque C (2017) Brain correlates of progressive olfactory loss in Parkinson's disease. Parkinsonism Relat Disord 41:44–50. https://doi.org/10.1016/j.parkreldis.2017.05.005

Cavaco S, Gonçalves A, Mendes A, Vila-Chã N, Moreira I, Fernandes J, Damásio J, Teixeira-Pinto A, Bastos Lima A (2015) Abnormal olfaction in Parkinson's disease is related to faster disease progression. Behav Neurol 2015:976589. https://doi.org/10.1155/2015/976589

Child KM, Herrick DB, Schwob JE, Holbrook EH, Jang W (2018) The neuroregenerative capacity of olfactory stem cells is not limitless: implications for aging. J Neurosci 38(31):6806–6824. https://doi.org/10.1523/jneurosci.3261-17.2018

Cho JH, Jeong YS, Lee YJ, Hong SC, Yoon JH, Kim JK (2009) The Korean version of the Sniffin' stick (KVSS) test and its validity in comparison with the cross-cultural smell identification test (CC-SIT). Auris Nasus Larynx 36(3):280–286. https://doi.org/10.1016/j.anl.2008.07.005

Del Tredici K, Braak H (2016) Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. Neuropathol Appl Neurobiol 42(1):33–50. https://doi.org/10.1111/nan.12298

Derjean D, Moussaddy A, Atallah E, St-Pierre M, Auclair F, Chang S, Ren X, Zielinski B, Dubuc R (2010) A novel neural substrate for the transformation of olfactory inputs into motor output. PLoS Biol 8(12):e1000567–e1000567. https://doi.org/10.1371/journal.pbio.1000567

Doty RL (2012) Olfactory dysfunction in Parkinson disease. Nat Rev Neurol 8(6):329–339. https://doi.org/10.1038/nrneurol.2012.80

Doty RL, Deems DA, Stellar S (1988) Olfactory dysfunction in Parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38(8):1237–1244. https://doi.org/10.1212/wnl.38.8.1237

Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI (1992) Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 55(2):138–142. https://doi.org/10.1136/jnnp.55.2.138

Fagundo AB, Jiménez-Murcia S, Giner-Bartolomé C, Islam MA, de la Torre R, Pastor A, Casanueva FF, Crujeiras AB, Granero R, Baños R, Botella C, Fernández-Real JM, Frühbeck G, Gómez-Ambrosi J, Menchón JM, Tinahones FJ, Fernández-Aranda F (2015) Modulation of higher-order olfaction components on executive functions

in humans. PLoS ONE 10(6):e0130319–e0130319. https://doi.org/10.1371/journal.pone.0130319
Fasano A, Herman T, Tessitore A, Strafella AP, Bohnen NI (2015) Neuroimaging of freezing of gait. J Parkinsons Dis 5(2):241–254. https://doi.org/10.3233/JPD-150536
Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD (2000) Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat Disord 6(3):165–170. https://doi.org/10.1016/s1353-8020(99)00062-0
Goldstein DS, Sewell L, Holmes C (2010) Association of anosmia with autonomic failure in Parkinson disease. Neurology 74(3):245. https://doi.org/10.1212/WNL.0b013e3181ca014c
Hawkes CH, Del Tredici K, Braak H (2007) Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol 33(6):599–614. https://doi.org/10.1111/j.1365-2990.2007.00874.x
Herman AM, Critchley H, Duka T (2018) Decreased olfactory discrimination is associated with impulsivity in healthy volunteers. Sci Rep 8(1):15584. https://doi.org/10.1038/s41598-018-34056-9
Hong SC, Yoo YS, Kim ES, Kim SC, Park SH, Kim JK, Kang SH (1999) Development of KVSS Test (Korean Version of Sniffin' Sticks Test). Korean J Otorhinolaryngol-Head Neck Surg 42(7):855–860
Hong S-M, Park I-H, Kim K-M, Shin J-M, Lee H-M (2011) Relationship between the Korean Version of the Sniffin' Stick Test and the T&T Olfactometer in the Korean Population. Clin Exp Otorhinolaryngol 4(4):184–187. https://doi.org/10.3342/ceo.2011.4.4.184
Hong JY, Sunwoo MK, Ham JH, Lee JJ, Lee PH, Sohn YH (2015) Apathy and olfactory dysfunction in early Parkinson's disease. JMD 8(1):21–25. https://doi.org/10.14802/jmd.14029
Huisman E, Uylings HB, Hoogland PV (2004) A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in Parkinson's disease. Mov Disord 19(6):687–692. https://doi.org/10.1002/mds.10713
Jordan LM, Liu J, Hedlund PB, Akay T, Pearson KG (2008) Descending command systems for the initiation of locomotion in mammals. Brain Res Rev 57(1):183–191. https://doi.org/10.1016/j.brainresrev.2007.07.019
Kim LH, Sharma S, Sharples SA, Mayr KA, Kwok CHT, Whelan PJ (2017) Integration of descending command systems for the generation of context-specific locomotor behaviors. Front Neurosci 11:581–581. https://doi.org/10.3389/fnins.2017.00581
Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S (1996) "Sniffin'' sticks": screening of olfactory performance." Rhinology 34(4):222–226
Kovacs GG, Klöppel S, Fischer I, Dorner S, Lindeck-Pozza E, Birner P, Bötefür IC, Pilz P, Volk B, Budka H (2003) Nucleus-specific alteration of raphe neurons in human neurodegenerative disorders. NeuroReport 14(1):73–76. https://doi.org/10.1097/00001756-200301200-00014
Lazarini F, Gabellec MM, Moigneu C, de Chaumont F, Olivo-Marin JC, Lledo PM (2014) Adult neurogenesis restores dopaminergic neuronal loss in the olfactory bulb. J Neurosci 34(43):14430–14442. https://doi.org/10.1523/jneurosci.5366-13.2014
Lee DH, Oh JS, Ham JH, Lee JJ, Lee I, Lee PH, Kim JS, Sohn YH (2015) Is normosmic Parkinson disease a unique clinical phenotype? Neurology 85(15):1270–1275. https://doi.org/10.1212/wnl.0000000000001999
Miyamoto T, Miyamoto M, Iwanami M, Hirata K, Kobayashi M, Nakamura M, Inoue Y (2010) Olfactory dysfunction in idiopathic REM sleep behavior disorder. Sleep Med 11(5):458–461. https://doi.org/10.1016/j.sleep.2009.09.013
Müller A, Reichmann H, Livermore A, Hummel T (2002) Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. J Neural Transm (vienna) 109(5–6):805–811. https://doi.org/10.1007/s007020200067
Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM (2002) Prevalence of olfactory impairment in older adults. JAMA 288(18):2307–2312. https://doi.org/10.1001/jama.288.18.2307
Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A (2011) Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 10(8):734–744. https://doi.org/10.1016/S1474-4422(11)70143-0
Palmer JL, Coats MA, Roe CM, Hanko SM, Xiong C, Morris JC (2010) Unified Parkinson's Disease Rating Scale-Motor Exam: inter-rater reliability of advanced practice nurse and neurologist assessments. J Adv Nurs 66(6):1382–1387. https://doi.org/10.1111/j.1365-2648.2010.05313.x
Pearce RK, Hawkes CH, Daniel SE (1995) The anterior olfactory nucleus in Parkinson's disease. Mov Disord 10(3):283–287. https://doi.org/10.1002/mds.870100309
Petzold GC, Hagiwara A, Murthy VN (2009) Serotonergic modulation of odor input to the mammalian olfactory bulb. Nat Neurosci 12(6):784–791. https://doi.org/10.1038/nn.2335
Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30(12):1591–1601. https://doi.org/10.1002/mds.26424
RexSoft (2018) Rex: excel-based statistical analysis software. Practiced Apr 2021 from http://rexsoft.org/
Roberts RO, Christianson TJH, Kremers WK, Mielke MM, Machulda MM, Vassilaki M, Alhurani RE, Geda YE, Knopman DS, Petersen RC (2016) Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurol 73(1):93–101. https://doi.org/10.1001/jamaneurol.2015.2952
Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, Launer L, White LR (2008) Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 63(2):167–173. https://doi.org/10.1002/ana.21291
Spildooren J, Vercruysse S, Desloovere K, Vandenberghe W, Kerckhofs E, Nieuwboer A (2010) Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning. Mov Disord 25(15):2563–2570. https://doi.org/10.1002/mds.23327
Stephenson R, Houghton D, Sundararajan S, Doty RL, Stern M, Xie SX, Siderowf A (2010) Odor identification deficits are associated with increased risk of neuropsychiatric complications in patients with Parkinson's disease. Mov Disord 25(13):2099–2104. https://doi.org/10.1002/mds.23234
Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25(15):2649–2653. https://doi.org/10.1002/mds.23429
Velayudhan L (2015) Smell identification function and Alzheimer's disease: a selective review. Curr Opin Psychiatry 28(2):173–179. https://doi.org/10.1097/yco.0000000000000146
Wenning GK, Shephard B, Hawkes C, Petruckevitch A, Lees A, Quinn N (1995) Olfactory function in atypical Parkinsonian syndromes. Acta Neurol Scand 91(4):247–250. https://doi.org/10.1111/j.1600-0404.1995.tb06998.x
Wilson RS, Arnold SE, Tang Y, Bennett DA (2006) Odor identification and decline in different cognitive domains in old age. Neuroepidemiology 26(2):61–67. https://doi.org/10.1159/000090250
Yoo HS, Chung SJ, Lee YH, Ye BS, Sohn YH, Lee PH (2020) Association between olfactory deficit and motor and cognitive function in Parkinson's Disease. J Mov Disord 13(2):133–141. https://doi.org/10.14802/jmd.19082