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Olfactory dysfunction and parasympathetic dysautonomia in Parkinson's disease

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Abstract

Objective—Olfactory impairment occurs early in Parkinson's disease (PD), as may dysautonomia. We investigated the relationship between olfaction and dysautonomia as well as other non-motor manifestations of PD.

Methods—Olfaction [University of Pennsylvania Smell Identification Test (UPSIT)], autonomic function in the pupillary (constriction and redilation velocity) and cardiac systems (resting low- and high-frequency heart rate variability (LF and HF HRV), positional changes in systolic blood pressure), neuropsychiatric function [Mini-mental Status Exam (MMSE)], Hamilton Depression Scale, activities of daily living [(ADLs), Schwab and England ADLs scale], quality of life [Short Form-36 health survey, PD Questionnaire 39 (PDQ-39)], and other non-motor symptoms [Non-motor Symptoms Scale (NMSS)] were simultaneously assessed in 33 participants (15 PD, 18 controls). Group comparisons, Spearman's coefficients and non-parametric rank-based regression were employed to characterize relationships between olfaction and non-motor features.

Results—Smell scores were lower in the PD group and correlated positively with pupil constriction velocity and HF HRV. Smell scores were correlated negatively with PDQ-39 and gastrointestinal items of the NMSS and positively with MMSE and Schwab and England ADLs. These correlated measures were not significant terms in regression models of smell scores in which age and PD diagnosis were significant and accounted for over half of the variability (R-squared 0.52–0.58).

Interpretation—This study suggests olfactory involvement occurs with parasympathetic dysautonomia in the pupillary and cardiovascular systems, involving both age-related and PD-related processes. Other non-motor features are concurrently involved, supporting the notion that aging and PD have widespread effects involving discrete portions of the autonomic and olfactory systems.

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Keywords

Parkinson's disease; Autonomic pathways; Dysautonomia; Olfaction

Introduction

Parkinson's disease (PD) is traditionally thought of as a disorder manifesting predominantly with motor dysfunction. However, pathologic and clinical studies have made it increasingly clear that non-motor deficits are also inherent to the pathophysiology of PD [1, 2]. Many of these observed deficits suggest dysfunction of autonomic pathways as well as their end organs and include orthostatic dizziness, constipation, urinary problems, erectile dysfunction, drooling, sweating, and swallowing problems. Deposition of α-synuclein, a protein that forms Lewy bodies which is a pathological hallmark of PD, has been found in both central and peripheral autonomic pathways, though their pattern of progression in PD has yet to be characterized [1]. Consequently, autonomic physiology in PD may provide additional clarification on the nature of PD as a multi-level widespread neurodegenerative process as PD pathology may directly lead to autonomic dysfunction.

Neurodegeneration in PD has also been shown to occur with early involvement of the olfactory bulbs [3]. Clinically, olfactory dysfunction has a prevalence of up to 90% in the PD population and often predates motor signs [4]. Therefore, its association with concomitant autonomic dysfunction may provide further insight into the pathophysiology of PD. Given that olfactory dysfunction in this patient population is well established and easily quantified, it further has potential to serve as an early marker for those at risk to develop PD and its accompanying non-motor features [4]. However, the relationship between olfaction and dysautonomia as well as other non-motor manifestations including neuropsychiatric disturbances, impairment of activities of daily living (ADLs) or quality of life (QOL) is unknown. Earlier and more comprehensive management of autonomic and other non-motor complications would greatly benefit PD patients, as these features contribute more to morbidity and decreased QOL than do the motor manifestations [1, 2, 5].

The primary purpose of this exploratory study is to characterize the relationships between olfactory dysfunction and dysautonomia in the pupillary and cardiovascular systems in PD. We also investigated whether associations exist between olfactory dysfunction and other concomitantly occurring non-motor deficits including depression, cognition, ADLs, and QOL. Finally, we explored whether age or PD status may underlie such associations, given that both are associated with olfaction, autonomic function, depression, cognition, ADLs and QOL.

Methods

Participants

Participants were recruited through the University of Pittsburgh Medical Center, whose IRB gave ethical approval. All participants signed informed consent. PD participants fulfilled the UK PD Society Brain Bank Clinical Criteria, scoring Hoehn and Yahr (HY) stage <5. Controls were age and sex matched. Exclusion criteria included: pyramidal and/or cerebellar signs, prior intracranial surgery, uncorrectable eyesight, bilateral cataract surgery, diabetes, uncontrolled hypertension, inability to participate from motor disability (HY = 5), taking medications affecting autonomic measures which could not be safely withheld, history of polyneuropathy, any other organic brain disorder including intracranial trauma or failure to pass a toxicology screen for substances that could influence results (alcohol, opiates, cocaine, cannabis, benzodiazepines, and amphetamines).

Design and measures

Measures assessed included age, sex, Folstein Mini-Mental State Exam (MMSE), Schwab and England ADLs scale, Short Form 36 (SF-36) health survey, Parkinson's Disease Questionnaire 39 (PDQ-39), Non-motor Symptoms Scale (NMSS), Hamilton Depression Rating Scale (HAM-D), HY stage, and the Unified Parkinson Disease Rating Scale Part III Motor Signs (UPDRS-III). The HY scale is a commonly used clinical rating metric for assessing progression of motor disability (range 0–5 with 0 being normal and 5 being most severely affected). The UPDRS-III is a valid and reliable measure of motor signs in PD including speech, tremor, rigidity, hand movements, posture, gait, stability and body bradykinesia. Each is rated on a zero-to-four scale (range of total UPDRS–III is 0–56, normal to most severe). Higher scores (ranges in parentheses) indicate greater impairment in the PDQ-39 (0–100), NMSS (0–360), HAM-D (0–52). Lower scores indicated greater impairment in the MMSE (0–30) and Schwab and England ADLs scale (0–100).

Olfaction was assessed with the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics Inc.). The UPSIT is composed of four booklets, each containing ten different odorants on separate pages. The participant is asked to identify the scent from a list of four choices. Smell scores are reported as total correct items out of 40.

Physiologic assessments were conducted in a room free of distracting stimuli at the same time every morning (0900 hours), same ambient temperature (22–24°C) in the same position. Autonomic measures were pupillary constriction and redilation velocity, heart rate variability (HRV) in low- (LF) and high-frequency (HF) bands, LF:HF HRV ratio, and positional changes in systolic blood pressure (SBP). Given the exploratory nature of the study, it was not clear that anti-parkinsonian medications could be withheld, so the first five PD participants were tested on medication. Subsequent participants withheld medications at least 12 h prior to testing. For pupillography, participants were seated in front of a monitor in darkness (illumination = 0.027 foot candles with monitor on). They were instructed to stare at a dim red fixation point (intensity < 0.03 cd/m^2) at eye level at a distance of 28.75″ subtending a visual angle of 0.25° for 11 min. After 3 min in darkness, 11 "flashes" (a white circle subtending a visual angle of 4.60°) were presented (1 s duration, every 10 s) at eye level at a distance of 73 cm with an intensity of 13 cd/m^2. The light reflex was separated from cardiac measures to avoid any cardiac-orienting responses. Stimuli were programmed with E-prime routines. ECG (modified lead II position) was sampled at 1,000 Hz utilizing Grass model 7 neurodata amplifiers. Resting ECG was recorded for 11 min during pupillography. LF and HF HRV were recorded. SBP was measured after the participant was in a supine position for 5 min and after the participant had been standing for 2 min.

Signal processing

All recordings were manually inspected for artifacts and proper signal processing. For pupillography, this consisted of removal of blink artifact and for ECG, removal of motion artifact and confirming R-wave detection. For light-reflex responses, the pupil response was averaged across the last ten trials. Constriction velocity was defined as velocity to minimum pupil diameter (mm/s) and redilation velocity as change in diameter divided by time elapsed from 50 to 75% redilation.

Statistical analyses

Two-sided *t*-tests (age, constriction velocity, LF HRV, supine and standing SBP, orthostatic SBP and SF-36), Fisher's exact test (gender), or Mann–Whitney *U* tests (all other variables) were used to compare groups. Effect sizes were calculated as Cohen's *d*. Combining data from PD and control groups, Spearman's rank correlation coefficients were used to investigate associations between olfaction and motor and non-motor measures. All statistical

modeling was done using nonparametric rank-based regression [6, 7]. Robust R-squared values were calculated [6, 7]. Associations between olfaction and motor as well as non-motor measures were investigated with age and PD status as covariates in the models. Tests for a modifying effect of PD were also performed. Levodopa equivalent dose (LED) was calculated for PD participants [8]. A secondary analysis of physiology measures compared PD participants for whom anti-parkinsonian medications were withheld and those for whom they were not. An $\alpha = 0.10$ was selected a priori as this exploratory study is intended to plan future research and generate hypotheses. Analyses were performed with SPSS Statistics 19 (IBM Corporation) and R 2.12.1 (The R Foundation for Statistical Computing).

Results

Group characteristics are summarized in Table 1. Age and gender were similar between the two groups. Smell scores were significantly lower in the PD group. Two cardiovascular measures were significantly lower (LF and HF HRV) and one was significantly higher (positional change in SBP) in PD compared to control groups. Standing SBP was significantly higher in the PD group relative to controls (147.0 vs. 127.8 mmHg, respectively, $p < 0.01$).

PD participants scored significantly higher on the HAM-D, PDQ-39 and NMSS and significantly lower on the Schwab and England ADLs scale and SF-36. Analyzing the aggregate of gastrointestinal (GI) related NMSS items only (drooling, dysphagia, constipation), the PD group scored significantly higher. There were no significant differences in any physiologic outcome measures among PD participants from whom anti-parkinsonian medications were withheld compared to those from whom they were not except for redilation velocity [0.38 (0.17) vs. 0.25 (0.09) mm/s, respectively, $p = 0.09$].

Correlations with UPSIT scores and nonparametric rank-based regression modeling for significant associations are summarized in Table 2. UPSIT scores were positively correlated with constriction velocity and HF HRV. Smell scores were negatively associated with age and PDQ-39 and positively correlated with Schwab and England ADLs score and MMSE. While UPSIT score was not associated with total NMSS score, it was negatively correlated with total score of GI items of the NMSS. Constriction velocity, HF HRV, PDQ-39, Schwab and England ADLs and MMSE were not significant terms in regression models with age and PD diagnosis in which the outcome was UPSIT score. Both age and PD diagnosis were significant, however, in all models and accounted for over half of the variability (Robust R-squared 0.52–0.58). There was no association between UPSIT and individual GI items on the NMSS. Although the combined correlation between smell score and LF:HF HRV ratio was not significant, a significant modifying effect of PD diagnosis was seen, such that the association was reversed in the PD compared to control groups ($r_S = 0.41$ vs. $r_S = -0.36$, respectively, $p = 0.06$). This modifying effect remained significant after adjusting for age. Within the PD group, olfaction was not significantly associated with UPDRS-III or HY stage. Because, combining data from both groups for correlations may introduce bias, we conducted supplementary analyses comparing correlations with smell score within each group. None of the significant combined group correlations differed significantly between groups.

Discussion

Our findings suggest that hyposmia is associated with pupillary and cardiovascular parasympathetic dysfunction as well as other non-motor deficits including GI dysfunction, cognition, ADLs and QOL in PD. Our regression models highlight the importance of accounting for age and disease status when associations among non-motor features in this

population are found, as the models suggest underlying these associations are aging and PD. Consistent with previous reports, olfactory impairment was more severe in PD compared to controls [9].

To our knowledge, a positive relationship between olfactory function and pupillary constriction but not redilation, has not been previously reported. This suggests that olfactory impairment is associated with parasympathetic, but not sympathetic pupillary dysfunction in PD.

Compared to controls, PD participants demonstrated lower HF and LF HRV, and greater changes in positional SBP. HF HRV, which reflects vagally mediated parasympathetic function, was positively associated with olfaction. Such an association was not found with LF HRV, a measure of both parasympathetic and sympathetic function, or change in positional SBP, which reflects sympathetic control of systemic vascular tone. Therefore, while PD participants had decreased parasympathetic and sympathetic cardiovascular function compared to controls, only parasympathetic dysfunction was associated with olfactory deficits. However, our regression analyses suggests that the associations observed are in large part due to age and PD-related processes as autonomic measures in themselves are not significant in a model of olfactory function which includes age and PD. Other work in a more advanced PD population compared PD patients with anosmia to those with milder olfactory deficits and demonstrated that sympathetic cardiovascular function was more impaired in anosmic PD patients [10]. In the context of our findings, one possible explanation is that olfactory dysfunction is associated with cardiovascular parasympathetic dysfunction early on in PD, and later neurodegeneration affects sympathetic function as well. Other work using ^{123}I-metaiodobenzylguanidine cardiac scintigraphy, a modality specific to sympathetic noradrenergic nerve terminals, demonstrated an association between olfaction and degeneration of sympathetic innervation in early PD, however, this degeneration may precede measureable physiological deficits such as orthostatic hypotension and impaired HRV [9, 11, 12]. The modifying effect of PD status found on the association between olfactory function and LF:HF HRV ratio suggests that pathologic changes affecting both sympathovagal balance and olfaction occur in PD but not in controls. Taken together, our pupillary and cardiovascular autonomic findings suggest that parasympathetic, but not sympathetic dysfunction coincides with olfactory impairment in the cohort of participants we tested with mild PD. Our regression models further suggest that age and PD-related processes largely account for the observed correlations (e.g., both PD-related neurodegeneration and aging simultaneously affect olfactory afferents and central parasympathetic centers).

We also found olfactory dysfunction to be associated with GI symptoms, which may further reflect distress related to autonomic degeneration in the GI tract. Olfactory disturbance was also associated with impairment in ADLs and cognition as well as decreased QOL. The association of olfaction with MMSE scores has been previously reported [11, 13]. However, as with autonomic measures, these non-motor measures were not significant terms in a model of olfactory function which included aging and PD diagnosis. This adds further evidence that olfactory dysfunction could be a marker for more global involvement of autonomic and other non-motor domains due to widespread effects of aging and PD-related multi-focal neurodegeneration. Consistent with previous work, we did not find a significant association between olfaction and depressive symptoms [14].

The relationship between olfactory dysfunction and severity of motor dysfunction in PD is not entirely clear [9–11, 13, 15]. In this study, no significant association was found between UPSIT scores and either UPDRS-III or HY stage. This suggests that the neuropathologic

processes contributing to progression of motor disability may not necessarily be occurring concomitantly with those leading to olfactory dysfunction.

Limitations of this study include its small sample size, cross-sectional design, limited range in PD severity and the possibility of residual effects of longer-acting anti-parkinsonian medications affecting results after withholding medications for 12 h. In addition, data quantifying cigarette smoking were not available and smoking status may affect olfactory and autonomic measures. Nevertheless, this work supports the feasibility of using smell testing as a marker for autonomic and other non-motor features, and provides further insight into our current understanding of PD pathophysiology and aging. Our results highlight the importance of accounting for age and disease status when associations among non-motor features in this population are found. As this is an exploratory study meant to generate hypotheses for future work, larger longitudinal studies are needed to establish the utility of olfactory and autonomic testing and further our understanding and treatment of autonomic and other non-motor manifestations of PD.

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References

1. Jain S. Multi-organ autonomic dysfunction in Parkinson disease. Parkinsonism Relat Disord. 2011; 17(2):77–83. [PubMed: 20851033]
2. Lim SY, Lang AE. The nonmotor symptoms of Parkinson's disease: an overview. Mov Disord. 2010; 25(Suppl 1):S123–S130. [PubMed: 20187234]
3. Braak H, Del Tredici K, Rub U, de Vos RA, Steur ENJ, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24(2):197–211. [PubMed: 12498954]
4. Doty RL. Olfaction in Parkinson's disease. Parkinsonism Relat Disord. 2007; 13(Suppl 3):S225–S228. [PubMed: 18267240]
5. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006; 5(3):235–245. [PubMed: 16488379]
6. Hettmansperger, T.; McKean, JW. Robust nonparametric statistical methods. 2. Chapman-Hall; New York: 2011.
7. Kloke, J.; McKean, J. RFit: rank estimation for linear models. R package version 0.11. 2011. (http://CRAN.R-project.org/package=Rfit)
8. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010; 25(15):2649–2653. [PubMed: 21069833]
9. Iijima M, Osawa M, Momose M, Kobayakawa T, Saito S, Iwata M, et al. Cardiac sympathetic degeneration correlates with olfactory function in Parkinson's disease. Mov Disord. 2010; 25(9): 1143–1149. [PubMed: 20131383]
10. Goldstein DS, Sewell L, Holmes C. Association of anosmia with autonomic failure in Parkinson disease. Neurology. 2010; 74(3):245–251. [PubMed: 20083801]
11. Oka H, Toyoda C, Yogo M, Mochio S. Olfactory dysfunction and cardiovascular dysautonomia in Parkinson's disease. J Neurol. 2010; 257(6):969–976. [PubMed: 20119648]
12. Haensch CA, Lerch H, Jorg J, Isenmann S. Cardiac denervation occurs independent of orthostatic hypotension and impaired heart rate variability in Parkinson's disease. Parkinsonism Relat Disord. 2009; 15(2):134–137. [PubMed: 18515170]
13. Stephenson R, Houghton D, Sundararajan S, Doty RL, Stern M, Xie SX, et al. Odor identification deficits are associated with increased risk of neuropsychiatric complications in patients with Parkinson's disease. Mov Disord. 2010; 25(13):2099–2104. [PubMed: 20669288]

14. Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. Biol Psychiatry. 1987; 22(12):1481–1485. [PubMed: 3676376]

15. Louis ED, Marder K, Tabert MH, Devanand DP. Mild Parkinsonian signs are associated with lower olfactory test scores in the community-dwelling elderly. Mov Disord. 2008; 23(4):524–530. [PubMed: 18098296]

Table 1

Participant characteristics and non-motor assessments

Participant characteristics	PD (*N* = 15)	Controls (*N* = 18)	*p*-value
Age	65.7 (12.3)	60.3 (13.5)	0.24
Number of women (%)	4 (26.7%)	9 (50.0%)	0.28
Hoehn and Yahr Stage	1.7 (0.6)	0	
UPDRS-III (motor)	10.7 (4.1)	0	
UPDRS total Score	19.1 (8.9)	0	
Mean levodopa dose equivalent (mg)	516 (376.7)	0	
Participants taking dopamine agonists (%)	5 (33.3%)	0	

Domain	Measure	PD	Control	Effect size	*p*-value
Olfactory	UPSIT smell score (total correct) *	20.7 (7.9)	31.4 (7.5)	1.16	< 0.01
Pupil	Constriction velocity (mm/s)	1.59 (0.40)	1.73 (0.52)	0.31	0.40
	Redilation velocity (mm/s)	0.34 (0.16)	0.26 (0.14)	0.53	0.83
Cardiovascular	LF HRV ($\times 10^{-1}$ s^2/Hz) *	6.8 (4.9)	13.7 (8.4)	0.88	0.02
	HF HRV ($\times 10^{-1}$ s^2/Hz) *	2.6 (1.8)	7.4 (5.3)	1.00	0.01
	LF:HF HRV ratio	2.63 (0.99)	2.32 (1.56)	0.23	0.26
	Positional change in SBP (mmHg) *	−15.53 (11.04)	−2.83 (11.75)	0.98	< 0.01
Depression	HAM-D *	6.6 (6.3)	2.5 (4.1)	0.74	0.01
Cognition	MMSE score	29.5 (1.0)	29.4 (1.3)	0.03	0.79
Activities of daily living	Schwab and England ADLs scale *	90.7 (8.8)	100 (0)	1.24	< 0.01
Non-motor symptoms	$NMSS^*_{total}$	17 (13.5)	2.4 (5.5)	1.19	< 0.01
GI-specific items	$NMSS_{GI}$ *	2.9 (3.4)	0.1 (0.2)	1.07	< 0.01
Quality of life	SF-36 Healthy Survey	32.1 (10.9)	18.8 (7.8)	1.17	< 0.01
	PDQ-39 Questionnaire	13.9 (9.2)	0.6 (2.4)	1.45	< 0.01

UPDRS Unified Parkinson disease rating scale, *UPSIT* University of Pennsylvania Smell Identification Test, *LF* low frequency, *HF* high frequency, *HRV* heart rate variability, *SBP* systolic blood pressure, *HAM-D* Hamilton depression scale, *MMSE* Folstein mini-mental status exam, *ADLs* activities of daily living, *NMSS* non-motor symptoms scale, *GI* gastrointestinal, *SF-36* Short Form 36 health survey, *PDQ-39* Parkinson's disease Questionnaire-39

* $p < 0.10$

Table 2

Spearman correlations and non-parametric regression with UPSIT smell score as outcome

Spearman correlations with UPSIT smell score			
Domain	**Non-motor feature**	**Spearman's ρ**	***p*-value**
Autonomic measures			
Pupil	Constriction velocity (mm/s) *	0.402	0.02
	Redilation velocity (mm/s)	−0.022	0.90
Cardiovascular	LF HRV ($\times 10^{-1}$ s^2/Hz)	0.274	0.18
	HF HRV ($\times 10^{-1}$ s^2/Hz) *	0.406	0.04
	LF:HF ratio	−0.66	0.75
	Positional change in SBP (mmHg)	0.16	0.38
Other features			
Age	Age in years	−0.532	< 0.01
Depression	HAM-D	−0.019	0.92
Cognition	MMSE	0.370	0.03
Activities of daily living	Schwab and England ADLs scale *	0.390	0.03
Non-motor Symptoms	$NMSS_{total}$	−0.254	0.15
GI-specific items	$NMSS^{*}_{GI}$	−0.364	0.04
Quality of life	SF-36 Healthy Survey	−0.226	0.21
	PDQ-39 Questionnaire *	−0.458	< 0.01
Parkinsonism (PD group only)	UPDRS-III (motor)	0.300	0.28
	Hoehn and Yahr Stage	0.278	0.32

Regression models of significant correlations, age and PD diagnosis with UPSIT smell score as outcome

Domain	**Predictors included in multivariable model**	**Significant terms**	**Robust R-squared**
Autonomic measures			
Pupil	Constriction velocity (mm/s), age, PD diagnosis	Age, PD diagnosis	0.53
Cardiovascular	HF HRV ($\times 10^{-1}$ s^2/Hz), age, PD diagnosis	Age, PD diagnosis	0.58
Other features			
Cognition	MMSE, age, PD diagnosis	Age, PD diagnosis	0.58
Activities of daily living	Schwab and England ADLs scale, age, PD diagnosis	Age, PD diagnosis	0.55
GI-specific items	$NMSS_{GI}$, age, PD diagnosis	Age, PD diagnosis	0.52
Quality of life	PDQ-39 Questionnaire, age, PD diagnosis	Age, PD diagnosis	0.55

UPDRS Unified Parkinson disease rating scale, *UPSIT* University of Pennsylvania Smell Identification Test, *LF* low frequency, *HF* high frequency, *HRV* heart rate variability, *SBP* systolic blood pressure, *HAM-D* Hamilton depression scale, *MMSE* Folstein mini-mental status exam, *ADLs* activities of daily living, *NMSS* non-motor symptoms scale, *GI* gastrointestinal, *SF-36* Short Form 36 health survey, *PDQ-39* Parkinson's disease Questionnaire-39, *PD* Parkinson's disease

* $p < 0.10$