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Olfactory dysfunction is associated with neuropsychiatric manifestations in Parkinson's disease

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Abstract

Background—Hyposmia, psychiatric disorders and cognitive problems are common non-motor manifestations in Parkinson's Disease but how they are related remains unclear.

Methods—To investigate the relationship between olfactory dysfunction and neuropsychiatric manifestations we performed a cross-sectional study of 248 patients at two movement disorders clinics at academic medical centers. Psychiatric measures were the Geriatric Depression Scale-15, Inventory of Depressive Symptomatology, State Anxiety Inventory, Apathy Scale and Parkinson's Psychosis Rating Scale. Cognitive measures were the Mini Mental State Examination, Hopkins Verbal Learning Test-Revised, Digit Span, Tower of London-Drexel and the Stroop Color Word Test. Olfaction was tested with the University of Pennsylvania Smell Identification test.

Results—There was no significant association between olfaction and mood measures, but psychotic symptoms were more common in patients with olfaction scores below the median (30% vs. 12%, $p<0.001$). Worse olfaction was associated with poorer memory (Hopkins Verbal Learning Test-Revised delayed recall items: mean(standard deviation) 6.2(3.2) vs. 8.4(2.8), $p<0.001$) and executive performance (Tower of London total moves, 52(38) vs. 34(21), $p<0.001$). Odor-identification score was a significant predictor of abnormal performance on these cognitive tests after adjustment for age, sex and disease characteristics in logistic regression models.

Conclusions—The relationship between hyposmia, psychosis, and specific cognitive impairments may reflect the anatomic distribution of Lewy pathology and suggests that olfactory dysfunction could be a biomarker of additional extranigral disease. Future prospective studies are warranted to assess whether hyposmia, a very early feature of Parkinson's disease, might be used to predict the appearance of other common non-motor symptoms.

Keywords

Parkinson's Disease; olfaction; non-motor symptoms; psychiatric symptoms; cognitive symptoms

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INTRODUCTION

Olfactory dysfunction (hyposmia) is a common non-motor symptom in Parkinson's disease (PD), with estimates of prevalence up to 80–90% (1, 2). Hyposmia is present early in disease and, in fact, may be one of the first manifestations of synucleinopathy, appearing years before the onset of motor symptoms (3–6). The high prevalence, persistence throughout disease, and ease of olfactory testing has fostered interest in the use of olfaction as a biomarker in PD for early diagnostic strategies, differential diagnosis, prediction of clinical outcomes and as a potential therapy-independent marker of disease progression (7, 8).

In some studies, olfactory dysfunction does not demonstrate a clear relationship with commonly used clinical measures such as Unified Parkinson's Disease Rating Scale (UPDRS) scores, Hoehn and Yahr stage or disease duration (9), at least when examined throughout the disease course. In contrast, other investigators have observed an inverse relationship between clinical variables and olfaction when odor discrimination or electrophysiologic variables were measured (10–12). Additionally, olfactory function does not appear to decline in a linear fashion with clinical progression of disease in individual patients, though some investigators have documented longitudinal worsening of olfactory performance at a group level (13–15). Taken together, these observations suggest a complex relationship between markers of olfaction and motor disability and whether hyposmia will ultimately prove a useful predictor of these features in PD remains unclear.

However, there is increasing interest in the relationship between hyposmia and other common non-motor symptoms in PD. For example, a recent report describes that clinical and physiologic markers of autonomic dysfunction were significantly worse in anosmic PD patients compared to those with only mild-moderate hyposmia (16) and hyposmia has been linked to decreased cardiac MIBG uptake in a Japanese population (17, 18). One recent report described associations between olfactory dysfunction, cognitive decline and visual hallucinations while another documented worse olfactory identification in apathetic versus non-apathetic patients (19, 20). However, these associations were established using retrospective chart review (20) or relatively small samples(19). Therefore, the goal of this study was to investigate the relationship between olfactory function, mood disorders, psychotic symptoms and cognitive function using a battery of established neuropsychiatric and cognitive instruments in a large cohort of PD patients.

METHODS

We performed a cross-sectional study of 248 PD patients at the Parkinson's Disease Research, Education and Clinical Center of the Philadelphia Veterans' Affairs Medical Center and the Parkinson's Disease and Movement Disorder Center of the University of Pennsylvania. This study represents a secondary analysis of data collected initially for a cross-sectional study of the epidemiology of neuropsychiatric aspects of PD. PD was determined clinically by a movement disorder neurologist consistent with a diagnosis of possible or probable PD by the Gelb criteria (21). Disease severity was measured using the Hohen and Yahr stage (22) and Unified Parkinson's Disease Rating Scale (UPDRS) Part III (23). Subjects were not instructed to alter their medication dosing and, therefore, were tested in their typical functional state. Olfactory function was tested by administration of the University of Pennsylvania Smell Identification Test (UPSIT) (24). A modified levodopa equivalent daily dosage (LEDD) including immediate and controlled release levodopa formulations and catechol-O-methyltransferase inhibitors was calculated as quantitative data were not available for all medications. All tests for each patient were performed at a single visit unless prohibited by fatigue or scheduling conflict.

Psychiatric assessments

The following psychiatric measures were used: 15-item Geriatric Depression Scale(GDS-15; scores 0–15, higher scores corresponding to greater depression) (25), Inventory of Depressive Symptomatology (26) (IDS; scores 0–84, higher scores indicating greater depression severity); the State Form of the Spielberger State-Trait Anxiety Inventory (27) (SAI; scores 20–80, higher scores indicating greater anxiety severity); and the Apathy Scale (28) (AS; scores 0 to 42, higher scores indicating greater apathy severity). Psychosis was assessed with a modified version of the Parkinson's Psychosis Rating Scale (29) (PPRS). A positive response to either the illusions or hallucinations item was coded as psychosis and analyzed as a dichotomous variable.

Cognitive assessments

Global cognitive function was assessed using the Mini Mental State Examination (30) (MMSE). The score on the delayed free recall component of the Hopkins Verbal Learning Task-Revised (31) (HVLT-R; scores 0–12, higher scores indicating better performance) was used as an indication of short-term memory. Executive functioning was assessed with the Tower of London-Drexel test (TOL-DX)(32), recording total moves required to complete the task, more moves indicating worse performance. An additional test of executive function was the inhibition condition of the Stroop Color Word Test (33) (SWCT). Attention was assessed with the backward score on the Digit Span subtest from the Wechsler Adult Intelligence Scale-Third Edition (34), which is thought to be more specific to attentional abilities and working memory compared with the forward Digit Span (35).

Statistical methods

Median UPSIT score (19) was used to divide the cohort into an upper and lower half based on olfactory identification performance (lower scores indicating worse olfaction). Differences in demographics (age, sex, smoking, education), disease characteristics (Hoehn and Yahr stage, UPDRS score, duration and LEDD) and neuropsychiatric test scores between the olfactory groups were determined using independent samples t-tests for scale variables or chi-squared tests for proportions. Non-parametric Mann-Whitney tests were also used for non-normally distributed variables (Hoehn and Yahr stage) with similar results (not shown). Backward logistic regression models were analyzed using an abnormal score on each of the neuropsychiatric tests (or the presence of illusions or visual hallucinations for psychosis) as the dependent variable with olfactory performance, age, sex, disease duration, Hoehn and Yahr stage and LEDD as independent variables for determination of odds ratios and 95% confidence intervals. Age-normalized scores ($T<35$, $Z<-1.5$ abnormal) were used for SCWT, HVLT-R and TOL-DX, therefore age was not included as a covariate in these models. Statistical analyses were performed using SPSS for Windows version 17.0.

RESULTS

Demographic and clinical characteristics of the cohort-relationship with olfactory function

The mean (SD) age of patients in this cohort was 64 (10) years and 186 (75%) subjects were male. Mean total UPSIT score was 20(7.4), and the median score was 19. Two-hundred thirteen (85%) subjects scored below the 25th percentile, adjusted for age and gender (36), in keeping with prior descriptions of the high prevalence of hyposmia in PD. Subjects below the median of olfactory function in our sample were older and more commonly male (Table 1). There was no significant difference in the proportion of smokers or years of education between olfactory groups (Table 1). Mean UPDRS-III scores and PD duration for the entire sample were 22(10) and 6.6(5.4) years, respectively. The median Hoehn and Yahr stage was 2 (interquartile range 2–2.5). UPDRS scores and Hoehn and Yahr stage were higher in

patients with worse olfactory function whereas there was no significant difference in disease duration between the groups (Table 1).

Psychiatric correlates of olfactory dysfunction in PD

We compared UPSIT performance with several well-characterized scales measuring depression, anxiety and apathy. In this cohort, mean score on the GDS-15 was 4.0(3.9) and 80 patients (33%) scored ≥5, suggesting clinically significant depressive symptoms. Mean score on the IDS was 18 (13) with 132 patients (52%) scoring in the "depressed" range (≥14). Mean score on the SAI was 40 (14), with 47 patients (16%) scoring>55, suggesting clinically relevant anxiety. The mean Apathy Scale score was 12(6.9), and 88 patients (37%) scored in the abnormal range (≥14). Mean scores on these mood scales did not differ significantly between patients with better or worse olfactory function (Table 1). With respect to items on the PPRS, patients with UPSIT scores below the median were more likely to report psychotic symptoms of visual hallucinations or illusions (Table 1), whereas auditory hallucinations (AH) were not significantly associated with UPSIT performance (11% of subjects in the bottom olfactory group reported AH vs. 7% in the top olfactory group, p=0.34)). UPSIT score was also a significant independent predictor of these psychotic symptoms in a logistic regression model that adjusted for age, sex and other clinical variables (Table 2).

Cognitive correlates of olfactory dysfunction in PD

We administered a variety of tests assessing global cognition (MMSE) and specific domains including attention (Digit Span), memory (HVLT-R) and executive function (SCWT and TOL-DX). In this cohort, mean score on the MMSE was 28(1.9) and 40(15%) of subjects scored below 27/30. SCWT mean score was 31(12) and 30(13% scored in the abnormal range. Mean reverse digit span was 6.8(2.5) with 50(21%) scoring <5. For MMSE, DS and SCWT, there were small (e.g. 28.0 vs. 28.6 for MMSE, Table 1) but statistically significant differences in mean score between olfactory groups ; however, olfactory performance was not a significant predictor of abnormal performance on these tests in logistic regression models adjusting for age, sex and disease characteristics. Mean score for the HVLT-R was 7.3(3.1) with 60(27%) of subjects scoring in the abnormal range. The mean total moves for TOL-DX was 43(32) and 54(22%) performed in the abnormal range. Mean scores on HVLT-R and TOL-DX were significantly worse in patients in patients with worse olfaction (Table 1), and UPSIT score below the median was associated with significantly increased odds of abnormal performance on these verbal memory (HVLT-R) and fronto-executive tasks (TOL-DX, Table 2).

DISCUSSION

Olfactory dysfunction is one of the earliest recognized signs of synucleinopathy in PD, and has garnered interest as a potential marker for other clinical manifestations that typically appear later in the disease course. In this study, we have examined the relationship of hyposmia to neuropsychiatric and cognitive outcomes in PD patients. Consistent with prior observations (9, 37), we found a high prevalence of olfactory dysfunction and a substantial fraction of patients in our cohort experienced clinically significant psychiatric symptoms(38). Global cognitive function, as measured by the MMSE, was relatively unaffected in our sample (mean 28), whereas tests of verbal memory and executive functions were abnormal in a significant proportion of our subjects. A small number of subjects had MMSE scores <24, however, excluding these patients from the analysis did not affect our results (not shown). These findings are consistent with prior descriptions of domain-specific cognitive dysfunction in non-demented PD patients(39, 40), and also reflect

the relative insensitivity of the MMSE for detection of mild cognitive impairment in PD (41, 42).

While the value of hyposmia as a biomarker of motor symptoms is currently unclear, our results, and those of others, increasingly support a link between olfactory dysfunction and non-motor symptoms. In particular, our results suggest an association between olfactory dysfunction and neuropsychiatric manifestations. Cramer and colleagues have described that apathetic PD patients exhibited worse olfactory performance than non-apathetic patients (19). While we observed trends toward higher levels of apathy and anxiety in patients with worse olfactory function, these did not reach statistical significance (Table 1); however, our studies used different instruments to measure both olfactory function and apathy. A recent retrospective cohort analysis by Stephenson *et al.* found that worse baseline olfactory function increased the risk of developing visual hallucinations (20). We also observed that psychotic symptoms, such as illusions or visual hallucinations, were significantly more common in patients with the worst olfactory function, and given the association between hallucinations and subsequent dementia, it seems possible that very poor olfaction may herald cognitive decline in PD.

Consistent with this idea, the report from Stephenson *et al.* also demonstrated an increased risk of incident cognitive dysfunction in patients with the worst baseline olfactory function (20). Cognitive problems were identified by a score of 2 (or 1 with corroborating chart documentation of the problem) on the corresponding UPDRS item and, therefore could not further differentiate the types of problems described or cognitive domains involved. Our data demonstrating an association of UPSIT score with performance on the HVLT-R and TOL-DX suggest the link may be specific to verbal learning as well as executive functions. In addition to these clinical findings, Bohnen and colleagues recently demonstrated that olfactory dysfunction was correlated with radiologic markers of cholinergic denervation in hippocampus and other cortical areas (43). Thus, evidence linking olfactory and cognitive dysfunction, along with potential neurochemical substrates, is developing rapidly.

The early onset of olfactory dysfunction in PD is subserved by the appearance of Lewy pathology in the olfactory system. Braak's detailed neuropathological analyses (44, 45) suggest that the olfactory bulb and lower brainstem may be induction sites from which Lewy pathology spreads through the midbrain and ultimately to cortical areas. An alternative "top-down" hypothesis has been advanced suggesting that olfactory connections could allow parallel spread both "up" to higher cortical areas and "down" to other recognized induction sites, such as, the dorsal motor nucleus of the vagus nerve (46). Variability in the pace and pattern of progression observed among different individuals with PD supports the idea that both mechanisms may coexist, and it is possible that early events in this process influence the route of pathological spread giving rise to clinical phenotypes including hallucinations or cognitive impairment (47). One interpretation of these results is that early, severe olfactory dysfunction may be a biomarker of additional extranigral disease, such as higher cortical Lewy pathology, leading to the development of hallucinations or cognitive dysfunction. Non-motor symptoms are increasingly recognized as common, treatment-refractory and disabling (48–50). Understanding early events that lead to non-motor features and, potentially the ability to predict their onset, could have tremendous clinical impact.

The results of our study must be interpreted in the context of several limitations. Using the UPSIT, we only interrogated odor identification whereas odor discrimination and threshold are also affected in PD, though there is some debate whether these tests all measure a common source of variance(51, 52). While our use of ten different neuropsychiatric instruments represents the first study to broadly investigate the relationship of hyposmia with specific psychiatric and cognitive domains, such an analysis necessarily introduces

concerns about the influence of multiple statistical testing. However, for those relationships that persisted after adjustment for covariates (psychosis, HVLT-R, TOL-DX), the group differences were most highly significant in the bivariate comparisons ($p<0.001$, Table 1). Additionally, a recent preliminary analysis in a small cohort (published as a letter to the Editor commenting on Bohnen's paper(43)) described a correlation between olfaction and verbal memory but not the MMSE (TOL-DX was not tested), supporting the association of hyposmia with specific cognitive domains as we observed.

The magnitudes of effect size we observed were relatively modest (adjusted ORs: 1.8–3.1). Verbaan *et al.* (53) found small but significant differences in scores between PD patients with and without olfactory impairment on the Scale for Outcomes in Parkinson's disease cognitive and psychiatric measures (SCOPA-COG, SCOPA-PC) in the PROPARK cohort but reported "no significant moderate or strong (>0.4) correlations" between olfactory impairment and other clinical domains, consistent with a small effect size. In their study, a relationship between individual cognitive domains and olfactory impairment, as we have observed, would potentially be minimized by use of an aggregate measure cognitive of function, such as the SCOPA-COG. While these results indicate that olfactory performance, along with other clinical variables, provides some information about neuropsychiatric manifestations (and vice versa), the strength of this relationship is presently unclear.

It is tempting to speculate that the association between olfactory dysfunction (a very early event) and typically later-occurring neuropsychiatric or cognitive phenotypes implies that hyposmia might be used predicatively. The data presented here are cross-sectional and cannot directly support such a claim. However, further prospective studies to determine whether early characteristics of olfactory impairment may predict future disease course are certainly warranted.

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DISCLOSURES

Dr. Morley has received travel funding from Teva Pharmaceutical Industries Ltd. Dr. Weintraub has served on a scientific advisory board for Boehringer Ingelheim; serves on the editorial board of *Movement Disorders*; has received speaker honoraria from Boehringer Ingelheim, ACADIA Pharmaceuticals, Novartis, Osmotica Pharmaceutical Corp., BrainCells Inc., Merck Serono, Sanofi-aventis, and Pfizer Inc; and has received/receives research support from Avid Radiopharmaceuticals, Inc., Boehringer Ingelheim, NIH (NIMH K23 MH067894 [PI], NINDS P50 NS053488-01 [Co-Investigator], NIA RO1AG031348 [Site PI], and NINDS R01NS065087 [Co-Investigator]), and from the Michael J. Fox Foundation for Parkinson's Research. Ms. Mamikonyan reports no disclosures. Dr. Siderowf serves on a scientific advisory board for and has received speaker honoraria from Teva Pharmaceutical Industries Ltd.; serves as a consultant for Supernus Pharmaceuticals, Inc.; and receives research support from Avid Radiopharmaceuticals, Inc., the NIH (NINDS U10 NS044451-023 [Site PI], NINDS P50 NS053488-01 [Co-Core Leader and Project Leader], NINDS R43NS0636071 [Site PI], and NINDS R01NS065087 [Co-Investigator]), and from the Institute for Neurodegenerative Disorders. Dr. Duda serves on a grant review panel for the Michael J. Fox Foundation for Parkinson's Research; receives research support from the U.S. Department of Veterans Affairs (Merit Award [PI]), the Michael J. Fox Foundation, and the Samueli Institute; and holds stock in C.R. Bard, Inc., Celgene, Clarient, Inc., and Johnson & Johnson.

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Table 1

Group differences in demographics, disease characteristics and psychiatric or cognitive measures based on odor identification performance

The cohort was divided in half based on the median UPSIT score. Lower UPSIT score implies worse performance. Data are expressed as mean(SD) for continuous measures or percentage of subjects (sex, smokers, psychosis). P-values for differences between groups are reported from independent samples t-tests for continuous measures or χ^2 tests for percentages. UPSIT, University of Pennsylvania Smell Identification Test. UPDRS, Unified Parkinson's Disease Rating Scale.

	UPSIT bottom (N=123)	UPSIT top (N=125)	p
UPSIT score	13(2.8)	26 (5.2)	<0.001
Demographic			
Age (years)	67(9.5)	63(10.3)	<0.001
Men(%)	84	66	0.001
Education (years)	16(2.9)	16(3.3)	0.20
Smokers(%)	4	6	0.41
Disease Characteristics			
Hoehn and Yahr Stage	2.3(0.71)	2.1(0.66)	0.001
UPDRS Part III	24(12)	20(8)	0.001
PD duration (years)	7.3(5.2)	6.0(5.4)	0.07
levodopa dose (mg)	580 (330)	450 (430)	0.01
Psychiatric			
Geriatric Depression Scale	3.8(4.0)	4.2(3.7)	0.45
Inventory of Depressive Symptomatology	19(12)	18(13)	0.30
State Anxiety Inventory	41(14)	39(15)	0.18
Apathy Scale	13(6.6)	12(7.1)	0.24
Psychosis (%)	30	12	<0.001
Cognitive			
Mini Mental State Examination	28(2.1)	29(1.6)	0.01
Digit Span	6.4(2.4)	7.2(2.6)	0.008
Stroop Color Word Test	29(12)	34(11)	0.001
Tower of London-DX	52(38)	34(21)	<0.001
Hopkins Verbal Learning Test-Revised	6.3(3.2)	8.4(2.8)	<0.001

Table 2

Poorer olfactory identification is associated with higher odds of psychotic symptoms and abnormal performance on tests of verbal memory or executive function

Odds ratios and p-values of having an abnormal score on the indicated tests after adjustment for age, sex, disease severity, duration and medication status. Backward logistic regression was performed with an abnormal score on the indicated test as the dependent variable and UPSIT performance (top or bottom half) together with the indicated covariates as independent variables. Age-specific standardized scores were available for the Stroop, Tower of London and Hopkins Verbal Learning Test, so age was not included as a covariate in the regression models for those tests. Covariates remaining significant at the p=0.05 level in the last iteration of the regression model are listed in the far-right column. UPSIT, University of Pennsylvania Smell Identification Test. LEDD, levodopa equivalent daily dose.

	Adjusted OR (95% CI) for UPSIT performance	p	Significant covariates at final iteration
Psychiatric			
Geriatric Depression Scale[a]	1.2 (0.70–2.3)	0.42	Hoehn/Yahr
Inventory of Depressive Symptomatology[a]	1.5 (0.86–2.7)	0.15	Hoehn/Yahr, sex
State Anxiety Inventory[a]	0.97 (0.47–2.0)	0.94	Hoehn/Yahr, age
Apathy Scale [a]	1.1 (0.61–1.9)	0.77	Hoehn/Yahr
Psychosis[a]	2.1 (1.0–4.3)	0.05	UPSIT, age, LEDD
Cognitive			
Mini Mental State Examination[a]	1.0 (0.47–2.1)	0.99	Hoehn/Yahr, age, sex
Digit Span[a]	1.0 (0.52–2.1)	0.90	Hoehn/Yahr, age
Stroop Color Word Test[b]	1.3 (0.50–3.2)	0.61	Hoehn/Yahr, sex, PD duration
Tower of London-DX[b]	3.1 (1.5–6.2)	0.001	UPSIT, Hoehn/Yahr
Hopkins Verbal Learning Test-Revised[b]	1.8 (1.1–3.7)	0.04	UPSIT, Hoehn/Yahr, duration

[a] Initial covariates in the regression model: UPSIT performance, age, sex, PD duration, Hoehn and Yahr stage, LEDD

[b] Initial covariates in the regression model: UPSIT performance, sex, PD duration, Hoehn and Yahr stage, LEDD.