Olfactory Dysfunction Evaluation Is Not Affected by Comorbid Depression in Parkinson's Disease

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ABSTRACT

Background: Olfactory function assessment is an important screening tool for Parkinson's disease (PD) diagnosis. It is debated whether olfaction is affected by comorbid depression. We assessed the relationship between depression and olfaction in PD and determined whether depression may limit the usefulness of olfactory testing for PD diagnosis.

Methods: Olfaction was evaluated using the Sniffin' Sticks test and the Hyposmia Rating Scale in four groups of subjects: PD patients without depression (n = 30); PD patients with major depression (PDD; n = 30); major depressive disorder (MDD) patients (n = 29); and healthy controls (HCs; n = 30).

Results: No differences were found between PD and PDD patients for total Sniffin' Sticks test, threshold, discrimination or identification scores, or in Hyposmia Rating Scale, although both groups differed from HCs and MDD patients ($P < 0.05$), which, in turn, showed similar olfactory scores.

Conclusions: Lack of differences in olfactory impairment between PD and PDD suggest that depression may not contribute to olfactory dysfunction in PD.

Key Words: Parkinson's disease; depression; olfactory dysfunction; premotor; nonmotor symptoms

Parkinson's disease (PD) patients present several nonmotor symptoms, including olfactory dysfunction and depression, which can be highly prevalent during all stages of the disease and may even develop before motor features onset.[1-3] Numerous attempts have been made to diagnose PD during the premotor phase through detection of nonmotor clinical markers.[4-6] Olfactory dysfunction evaluation is useful, ultimately enriching the yield of screening batteries in at-risk populations.[6-8] Olfactory impairment assessment therefore contributes to differentiation of PD from other parkinsonisms.[9-11]

Olfactory dysfunction frequency averages 75%.[12] Degree of impairment appears to be independent of disease duration or severity.[13-15] Neuropathological substrates underlying olfactory dysfunction include involvement of the olfactory bulb, the anterior olfactory nucleus, and/or olfactory-related cortices.[16,17] Olfactory impairment can be assessed by means of objective tests, such as the Sniffin' Sticks Test (SST)[18] or University of Pennsylvania Smell Identification Test (UPSIT),[19] as well as by subjective tests, such as the simple, self-administered Hyposmia Rating Scale (HRS).[20]

The relationship between olfactory impairment and other common clinical features of PD has not been studied in depth.[15,21,22] Furthermore, somatic symptoms of depression may mimic incipient PD posing a diagnostic dilemma, especially when olfaction is impaired in patients with major depressive disorder (MDD).[23-27] The aim of this study was to determine whether olfactory function is altered in the presence of depression and therefore whether depression may limit the usefulness of olfactory testing for PD diagnosis.

Patients and Methods

The protocol conformed to Helsinki Declaration principles and was approved by the local institutional review board. All participants gave written informed consent before study entry.

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Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Funding agencies: Malco Rossi received a scientific initiation scholarship from the Florencio Fiorini Foundation and from the Argentine Medical Association for this study.

Received: 11 February 2015; **Revised:** 28 April 2015; **Accepted:** 29 April 2015

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26276

Study Sample

Sixty consecutive unselected PD patients diagnosed following UK Parkinson's Disease Society Brain Bank criteria[28] were recruited from a tertiary outpatient movement disorders clinic together with 29 consecutive unselected patients fulfilling Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for unipolar MDD, recruited from a tertiary outpatient psychiatry clinic at the same institution. A group of 30 age- and gender-matched healthy controls (HCs) were selected among PD patient relatives. Subjects with a history of chronic sinusitis or current rhinorrhea and significant exposure to volatile substances were excluded, as were individuals who suffered head trauma with loss of consciousness, referred history of drug abuse, nasal surgery, or were current smokers. PD patients with previous functional brain surgery, bipolar disorder, apathy, or psychosis were excluded.

Evaluation

PD patients were evaluated during the *on* state. Levodopa daily equivalent dosage (LDED) was calculated according to conversion formulae.[29] Depression was rated using the Beck Depression Inventory (BDI; cut-off score: 17) and Hamilton Depression Rating Scale (HAM-D). Cut-off scores in patients with and without PD were set according to International Parkinson and Movement Disorder Society (MDS) Task Force guidelines.[30] Neurological examination of MDD patients and HCs was conducted to search for parkinsonism. Anxiety was evaluated using the Beck Anxiety Inventory (BAI) and Hamilton Anxiety Rating Scale (HAM-A). HAM-A and HAM-D were not conducted in HCs because BDI and BAI were used for screening purposes. The Montreal Cognitive Assessment was performed in all patients to rule out dementia (cut-off score: 24), a diagnosis that could ultimately alter olfactory evaluation results.

Olfactory Testing

Olfactory function was evaluated using the extended version of the SST (Burghart Messtechnik, Wedel, Germany)[18] and the HRS.[20] The former consists of three test subsets containing felt-tip whiteboard markers that assess different olfaction modalities, such as threshold, discrimination, and identification. Hyposmia diagnosis is defined as the 10th percentile of total SST score. Functional anosmia is diagnosed when total score is $\leq$16.5.[31] The HRS contains six Likert-type self-administered questions referring to frequency with which certain recognizable every day odors are usually perceived. Olfaction was investigated in a cross-sectional design that enrolled subjects with PD, PD patients with major depression (PDD), MDD, and HCs.

Statistical Analysis

Categorical data were compared using a chi-square test, and numerical variables were analyzed using Wilcoxon-Mann-Whitney's test. Analysis of covariance (ANCOVA) adjusted for age and gender was conducted, followed by a post-hoc Bonferroni's test to compare olfactory function among groups. Spearman's correlation test was employed to correlate PD disease duration and severity of depression (BDI and HAM-D) with total SST score. Descriptive data are presented as mean $\pm$ standard error of the mean (SEM) or proportions. Alpha was set at 0.05.

Results

Demographics and Clinical Assessment

No significant differences in age, gender, education, and disease duration were found between groups, or between PD and PDD patients. Patients with PDD showed increased MDS-UPDRS-I ($P = 0.01$), MDS-UPDRS-II ($P = 0.05$), MDS-UPDRS-III ($P = 0.04$), and LDED ($P = <0.01$) values and reduced use of dopamine agonists ($P = 0.01$), in comparison to PD patients, but no differences in L-dopa use. Antidepressant use was lower in PDD than in MDD patients ($P < 0.001$). Table 1 summarizes subject demographics, medications, and clinical features.

Olfaction Assessment

No significant differences were found between PD and PDD in total SST, threshold, discrimination, or identification scores or the HRS, although both PD groups differed from HC and MDD patients ($P < 0.05$). No significant correlations were found between PD disease duration and total SST ($r = -0.03$; $P = 0.8$), threshold ($r = 0.08$; $P = 0.5$), discrimination ($r = 0.06$; $P = 0.7$), or identification ($r = -0.2$; $P = 0.2$) scores or HRS ($r = 0.001$; $P = 0.9$). Olfactory function evaluation according to total SST, threshold, discrimination, and identification subsets, as well as HRS, was similar between MDD patients and HCs (Table 2). Severity of depression according to BDI and HAM-D in both the two PD ($r = -0.01$; $P = 0.5$ for BDI; $r = -0.04$; $P = 0.8$ for HAM-D) and two non-PD groups ($r = 0.3$; $P = 0.1$ for BDI; $r = 0.2$; $P = 0.3$ for HAM-D) combined was not related to total SST score.

Eight (28%) MDD patients showed olfactory impairment based on total SST score (threshold was affected in 5 patients, discrimination in only 2, and identification in 7), and this profile was similar to that observed in PD or PDD patients. Severity of depression according to BDI and HAM-D in hyposmic MDD patients was not related to total SST score ($r = 0.4$; $P = 0.3$ for BDI and $r = -0.5$; $p = 0.1$ for HAM-D). Somatic motor features (speech disturbance,

TABLE 1. Patient demographic and clinical features

	HC (n = 30)	MDD (n = 29)	PD (n = 30)	PDD (n = 30)	*P* Value
Males (%)	14 (47)	7 (24)	15 (50)	14 (47)	0.2
Age, years	63.4 ± 1.8	65.6 ± 2.2	62.7 ± 1.6	68.3 ± 1.9	0.1
Education, years	13.3 ± 0.7	13.2 ± 0.3	13.6 ± 0.6	12.5 ± 0.7	0.6
PD disease duration, years			3.7 ± 0.7	4.4 ± 0.7	0.5
MDS-UPDRS-I			4.7 ± 1.0	8.3 ± 0.9	0.01
MDS-UPDRS-II			5.1 ± 1.1	10.5 ± 1.1	0.03
MDS-UPDRS-III			17.7 ± 1.7	24.4 ± 1.7	<0.01
H & Y stage, median			2	2	
L-dopa use (%)			15 (50)	23 (77)	0.06
Dopamine agonist use (%)			25 (83)	16 (53)	0.01
LDED			327.2 ± 74.0	660.0 ± 72.3	<0.01
BDI	2.7 ± 1.4	15.5 ± 1.3	6.7 ± 1.1	14.6 ± 1.1	0.7 *P* < 0.05 vs. HC *P* < 0.05 vs. MDD *P* < 0.05 vs. PDD *P* < 0.05 vs. PD
HAM-D		16.5 ± 1.8	6.8 ± 2.2	16.5 ± 1.7	0.8 *P* < 0.05 vs. MDD *P* < 0.05 vs. PDD *P* < 0.05 vs. PD
Antidepressant use (%)		27 (93)		9 (30)	<0.001
BAI	3.9 ± 2.3	8.7 ± 1.8	9.8 ± 1.6	13.8 ± 1.6	0.3 *P* < 0.05 vs. HC
HAM-A		12.2 ± 1.7	8.1 ± 2.3	13.5 ± 1.3	0.5
MoCA	29.0 ± 0.7	28.7 ± 1.2	28.1 ± 1.5	27.5 ± 1.3	0.4
FAB		23.5 ± 1.0	24.3 ± 0.9	22.5 ± 0.8	0.5

Chi-square followed by z-score adjustment with Bonferroni's test for categorical variables. Mean ± SEM (ANCOVA adjusted for age and gender and followed by Bonferroni's test for >2 group comparisons and Wilcoxon-Mann-Whitney's test for two group comparisons). *P* value reported tests for main group effect.

rigidity, intention and postural hand tremor, rest tremor, body and limb bradykinesia, flexed posture, gait impairment, freezing of gait, and postural instability) of patients with MDD and olfactory dysfunction were not different from those of MDD patients with normal olfactory function.

Discussion

The main finding of the present study is that depression does not affect olfaction, which is a significant emerging tool in the early diagnosis of PD. As expected, PD patients showed poorer olfactory function, compared to HCs. Depressed PD patients showed similar olfactory threshold, discrimination, and identification deficits to those of nondepressed PD patients, suggesting that olfaction behaves as an independent factor from comorbid depression. Hyposmia was present in 8 (28%) MDD patients, of which 3 (10%) had functional anosmia.

Findings have implications for olfactory function assessment at early motor disease stages or during the premotor phase, when specific nonmotor features, such as olfactory dysfunction and depression, may

TABLE 2. Olfactory performance comparison between groups

	HC (n = 30)	MDD (n = 29)	PD (n = 30)	PDD (n = 30)	*P* Value
SST-Threshold	5.6 ± 0.4	4.6 ± 0.5	1.6 ± 0.5	2.3 ± 0.5	*P* < 0.05 vs. HC and MDD
SST-Discrimination	12.0 ± 0.5	11.2 ± 0.6	7.8 ± 0.5	6.6 ± 0.5	
SST-Identification	12.4 ± 0.5	10.6 ± 0.6	5.9 ± 0.5	5.9 ± 0.5	
SST-Total	30.1 ± 1.2	26.5 ± 1.4	15.4 ± 1.2	14.8 ± 1.2	
HRScale	23.6 ± 0.8	22.6 ± 0.9	19.2 ± 0.8	18.2 ± 0.8	
Hyposmia (%)[a]	1 (3)	8 (28)	23 (76)	24 (80)	
Functional anosmia (%)[b]	0 (0)	3 (10)	16 (53)	14 (47)	

Mean ± SEM (ANCOVA adjusted for age and gender and followed by Bonferroni's test). Chi-square followed by z-score adjustment with Bonferroni's test for categorical variables. *P* value reported tests main group effect.
[a]Score at 10th percentile (%) of total SST.
[b]Defined as total SST <16.5.

develop in the absence of motor features.[1-3] Because depression may coexist with olfactory dysfunction in the premotor phase of PD, both probably representing early limbic phenotypes of the disorder, our findings are important in that they seem to rule out comorbid depression as a confounding factor for olfactory dysfunction evaluation in PD.

One previous study found that higher levels of depression symptoms in PD assessed using BDI were associated with worse UPSIT scores.[22] However, results from our study are in line with a different study using BDI and SST,[15] as well as with a previous cross-sectional study in 248 PD patients that found no significant differences in mood measures between patients with better or worse olfactory function according to UPSIT.[21] Our study differed from two of the previously mentioned in the way we used SST, which evaluates threshold and discrimination modalities in addition to identification, the unique modality covered by UPSIT.

In MDD patients evaluated with BDI,[24,25] olfactory sensitivity measured using threshold tests was reduced in one study, but unaffected in another,[27] similar to our results. Identification was found to be compromised in MDD patients using SST in one study,[26] in contrast to our results and those of most published studies that failed to find any difference between depressed patients and healthy individuals.[23,25,27] In 85 nondemented healthy older adults[32] and in 278 consecutive healthy adults with olfactory impairment,[33] depressive symptoms were not associated with deficits in SST thresholds or identification modalities. Possible discrepancies among studies evaluating the relationship between olfaction and depression may be owing to one of the following: lack of standardized measures of olfaction or depression; varying levels of depression severity; and small sample size.

Olfactory impairment in the 8 MDD patients identified was mainly owing to threshold and identification deficits. Somatic features were not different between MDD patients with normal or abnormal olfactory function. These patients may still develop PD in the future, and a dopaminergic-imaging scan would have been useful.

A secondary observation of the current study was lower use of dopamine agonists in PDD patients, compared to PD patients, which may suggest a direct antidepressant effect of these agents.[34] We also found, as in other studies,[35-37] less use (30%) of antidepressants in PDD patients, compared to MDD patients, that cannot be explained in our sample by higher dopamine agonist use and is in agreement with a recent study showing that antidepressant use in PD is not affected by concomitant dopamine agonist treatment.[38] This reflects poor recognition and poor management of depression in PDD patients (despite showing significantly higher scores in BDI, in comparison to PD patients), mainly owing to overlapping of motor and mood symptoms.[39]

At first glance, this study appears to be limited by a higher presence of women in the MDD group. Some previous studies found that women outperformed men on olfactory function.[31,40] This limitation was overcome by correcting for gender bias. Another limitation might be a floor effect that limits seeing any further diminution of olfactory scores by comorbid depression. Finally, PDD patients were not diagnosed according to the DSM-5 criteria for MDD, but self-report measures.

In conclusion, olfactory impairment in MDD occurs less often and is less severe in magnitude, but is similar in profile to that observed in PD and PDD patients. Lack of quantitative or qualitative differences between PD and PDD suggest that depression does not contribute to olfactory dysfunction in PD. Thus, the present results indicate that olfactory testing for PD diagnosis may not be altered by the presence of comorbid depression. ■

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