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Brain correlates of progressive olfactory loss in Parkinson's disease

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ABSTRACT

Background: Olfactory dysfunction is present in a large proportion of patients with Parkinson's disease (PD) upon diagnosis. However, its progression over time has been poorly investigated. The few available longitudinal studies lack control groups or MRI data.
Objective: To investigate the olfactory changes and their structural correlates in non-demented PD over a four-year follow-up.
Methods: We assessed olfactory function in a sample of 25 PD patients and 24 normal controls of similar age using the University of Pennsylvania Smell Identification test (UPSIT). Structural magnetic resonance imaging data, obtained with a 3-T Siemens Trio scanner, were analyzed using FreeSurfer software.
Results: Analysis of variance showed significant group ($F = 53.882$; $P < 0.001$) and time ($F = 6.203$; $P = 0.016$) effects, but the group-by-time interaction was not statistically significant. UPSIT performance declined $\geq$1.5 standard deviations in 5 controls and 7 patients. Change in UPSIT scores of patients correlated positively with volume change in the left putamen, right thalamus, and right caudate nucleus.
Conclusion: Olfactory loss over time in PD and controls is similar, but we have observed significant correlation between this loss and basal ganglia volumes only in patients.

1. Introduction

Olfactory dysfunction is very frequent in PD. This impairment can already be observed in *de novo* patients, and is unrelated to dopaminergic treatment [1]. In a multicenter study, the prevalence of olfactory deficits was estimated to be 96.7% when compared with young subjects, and 74.5% when adjusted for age [2]. However, the degree of olfactory impairment in PD can range from normal to severe hyposmia. It has been suggested that normosmic patients could be a unique clinical phenotype with fewer motor deficits and a more benign disease course [3]. In contrast, severe olfactory dysfunctions have been associated with worse cognitive performance, more cognitive decline over time, and higher risk of progression to mild cognitive impairment (MCI) and to dementia [4–6].

Olfactory impairment is observed in *de novo* patients and can therefore occur regardless of dopaminergic treatment [7,8]. Olfactory dysfunction has also been found to be a preclinical or premotor manifestation in PD [1,9]. In a study of asymptomatic relatives of PD patients, it has been found that hyposmia is associated with a 12.5% risk of developing PD within a five-year period [10]. Similarly, patients diagnosed with idiopathic anosmia are at a higher risk of developing PD [11]. Moreover, hyposmia is observed in patients with idiopathic REM sleep behavior disorder, a prodromal PD symptom [12].

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The progression of olfactory deficits in PD is unclear. Cross-sectional studies are inconsistent, with some suggesting that olfactory loss does not progress over the course of PD since it does not correlate with disease duration [1,13,14]. Nonetheless, correlations with disease severity and symptom duration was also reported [15]. The lack of worsening in olfaction is consistent with Braak staging describing the olfactory bulb as a region affected in the first stages of the disease [16]. However, the progression of degenerative changes in other regions involved in olfaction might contribute to increase the degree of olfactory impairment. Results from post-mortem studies revealed pathological changes (Lewy body formation) in the olfactory bulb but also in other brain regions such as the anterior olfactory nucleus, the piriform cortex, the amygdaloid complex, the entorhinal cortex, and the hippocampal formation [1]. In agreement with the involvement of several regions explaining olfactory deficits in PD, MRI studies have reported correlations of olfactory deficits with olfactory bulb volume [17–19], but also with piriform and orbitofrontal cortical volumes [20,21].

To the best of our knowledge, only three longitudinal studies of olfactory deficits in PD have been published [22–24]. These studies did not include a control group, which makes it difficult to distinguish disease-related decline from the effects of aging on olfactory function [25]. Moreover, there are no previous longitudinal studies including MRI data. In the current work, we investigated the olfactory changes in a sample of patients compared with a control group of similar age. We also performed correlation analyses between olfactory loss and measures of brain atrophy.

2. Method

2.1. Participants

The study sample included 25 PD patients and 24 healthy controls (HC) who underwent olfactory and MRI evaluation twice. These subjects are part of a cohort of 98 PD patients and 33 HC recruited between October 2010, and March 2012. In the present study, we only included subjects who underwent olfactory and MRI evaluation at both time points. In the 2010 cohort, the UPSIT was only administered to a small subsample. The mean (±standard deviation) follow-up interval was 44.9 ± 5.7 months for patients and 45.9 ± 3.5 months for controls ($F = 0.732$; $P = 0.468$). Inclusion criteria for patients at time 1 were: (1) the fulfillment of UK PD Society Brain Bank diagnostic criteria for PD; (2) no surgical treatment with deep brain stimulation. Exclusion criteria were: (1) dementia according to Movement Disorders Society criteria; (2) Hoehn and Yahr (H&Y) score > 3; (3) significant psychiatric, neurological, or systemic comorbidity; (4) low global intelligence quotient estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (scaled score ≤ 7); (5) Mini Mental State Examination (MMSE) score < 25; (6) presence of claustrophobia; (7) significant pathological MRI findings other than mild white matter hyperintensities in the FLAIR sequence; (8) MRI artefacts.

All PD patients were taking antiparkinsonian medication consisting of different combinations of L-DOPA, COMT inhibitors, MAO inhibitors, dopamine agonists, and amantadine. In order to standardize doses, levodopa equivalent daily dose (LEDD) was calculated as suggested by Tomlinson et al. [26] All assessments were done in the *on* state. Motor disease severity was evaluated using H&Y staging and the Unified Parkinson's Disease Rating Scale motor section (UPDRS-III).

The study was approved by the Ethics Committee of the University of Barcelona (IRB00003099). All subjects provided written informed consent to participate after full explanation of the procedures involved.

2.2. Olfactory and clinical assessment

Odor identification was assessed using the Spanish version of the University of Pennsylvania Smell Identification Test [27]. The UPSIT is a standardized multiple-choice scratch-and-sniff test consisting of four test booklets with 10 items each. Subjects scratched the impregnated area and were asked to select from one of four possible answers for each item. If the patient could not identify an odor, and the examiner observed that the area was not sufficiently scratched, the examiner either scratched the area or suggested that the patient do so until an odor was selected. Subjects were also asked for their smoking history and whether they were aware of having any smell dysfunction. Following normative data presented in the UPSIT manual, which includes adjustment for age and sex, scores greater than 33 in males and 34 in females were considered to reflect normosmia, and scores lower or equal to 18 reflected anosmia. Olfactory decline was established if the total UPSIT score was at least 1.5 standard deviation (based on the distribution of scores in the HC group at baseline) lower at time 2 than at time 1.

Participants were assessed with a neuropsychological battery recommended by the Movement Disorder Society task force to evaluate cognitive functions in PD [28]. Attention and working memory were assessed with the Trail Making Test (TMT) (in seconds), part A (TMT A) and part B (TMT B), Digit Span Forward and Backward, and the Stroop Color-word Test and Symbol Digits Modalities Tests (SDMT); executive functions were evaluated with phonemic (words beginning with the letter “p” in 1 min) and semantic (animals in 1 min) fluencies; language was assessed by the total number of correct responses in the short version of the Boston Naming Test; and memory through total learning recall (sum of correct responses from trial I to trial V) and delayed recall (total recall after 20 min) using Rey's Auditory Verbal Learning Test (RAVLT). Visuospatial and visuoperceptual functions were assessed with Benton's Judgement of Line Orientation (JLO) and Visual Form Discrimination (VFD) tests.

As in a previous study [29], the presence of MCI was established if the z-score for a given test was at least 1.5 lower than the expected score in at least two tests in one domain, or in at least one test per domain in at least two domains. Furthermore, the presence of dementia was determined if MMSE score was below 25, or if there was cognitive impairment in more than one domain and impaired instrumental activities of daily living (IADL), as recommended by Dubois et al. [30].

The Beck Depression Inventory II, Starkstein's Apathy Scale, and the Neuropsychiatric Inventory were administered to all subjects to explore the presence of psychiatric symptoms.

2.3. MRI analyses

2.3.1. Preprocessing of longitudinal imaging data

MRI data were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany) at both times. The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, 240 slices, FOV = 256 mm; 1 mm isotropic voxel) and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

Cross-sectional preprocessing of both times was performed using the automated FreeSurfer stream (version 5.1; available at: http://surfer.nmr.harvard.edu) as previously described in Segura et al. [29]. Detailed information about the longitudinal FreeSurfer stream is described in Ibarretxe-Bilbao et al. [31].

Longitudinal cortical thickness comparisons were performed using the longitudinal two-stage model. In this analysis, we computed the symmetrized percent of change (SPC) of cortical

thickness. Cortical thickness SPC is the rate in mm/year (*((thickness2-thickness1)/(time2-time1))* with respect to the average thickness (*0.5*(thickness1+thickness2)*). In aging or disease, SPC is expected to be negative in most regions (https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalTwoStageModel). We also obtained striatal (putamen and caudate) volumes via whole-brain segmentation.

Comparisons between groups were performed using a vertex-by-vertex general linear model. One-sample t-tests were performed to test time effects in both groups (if the SPC was different from zero). To test group-by-time interaction effects, SPC was included as a dependent factor and group as an independent factor (Supplementary Table 1).

In addition, supplementary cross-sectional intergroup cortical thickness comparisons were performed using a vertex-by-vertex general linear model with FreeSurfer at time 1 and time 2 (Supplementary Table 1).

All results were corrected for multiple comparisons using pre-cached cluster-wise Monte Carlo simulation with 10,000 iterations. Simulation was applied for negative time effects (time 2 < time 1) in each group, whereas, on all other models, simulation was applied for absolute results. Reported cortical regions reached one-tailed and two-tailed corrected significance level of $p < 0.05$ respectively.

The SPC of striatal volumes was computed and introduced in independent t-tests in order to compare it between groups. Significant results were corrected by general cognitive status (MMSE), age and gender. The SPC of UPSIT scores was also calculated. Pearson's correlation test was used to study the relationship between SPC of striatal volumes and SPC of UPSIT scores, and control of the false-discovery rate to 5% (FDR) was used to correct for multiple testing [32].

2.4. Statistical analyses of demographic, clinical, and olfactory data

Statistical analyses of demographic, clinical, and olfactory data were performed using IBM SPSS Statistics 22.0.0 (2013; Armonk, NY: IBM Corp). Group differences in demographic and clinical variables between HC and PD patients were analyzed with independent t-tests for quantitative measures or with Pearson's chi-squared test for categorical measures. Mann-Whitney's *U* test was used when comparing PD with olfactory decline and PD non-decliners, due to small subsamples. In order to study the relationship between clinical and olfactory data, Pearson's correlation coefficient test was used. Group-by-time interaction effects in clinical variables such as UPSIT, neuropsychological tests, and neuropsychiatric symptoms between PD and HC were assessed through a repeated-measures general linear model.

3. Results

3.1. Demographic and clinical characteristics

There were no differences between groups in age ($t = 1.468$; $P = 0.149$), years of education ($t = 1.235$; $P = 0.223$), estimated IQ scores ($t = 1.045$; $P = 0.301$), or sex ($X^2 = 0.506$; $P = 0.477$). Regarding psychiatric symptoms, there were no significant interactions between group and time in Beck Depression Inventory II ($F = 1.777$; $P = 0.190$), Starkstein's Apathy Scale ($F = 0.090$; $P = 0.766$), or in Cummings' Neuropsychiatric Inventory scores ($F = 0.992$; $P = 0.325$) (Table 1).

Significant interactions between group and time were found in Stroop Color ($F = 5.445$; $P = 0.024$), Stroop Word-Color ($F = 5.121$; $P = 0.029$), SDMT ($F = 8.107$; $P = 0.007$), and the short version of the BNT ($F = 5.077$; $P = 0.029$). At follow-up, PD-MCI criteria were fulfilled by 12 (25%) patients, from whom 6 were cognitively preserved at baseline. Two (4.1%) PD-MCI patients had converted to PD dementia at follow-up.

3.2. Olfactory decline over time

Table 2 shows the UPSIT performance at baseline and after four years of follow-up. The distribution of the degree of impairment in PD patients in the first assessment was 36% anosmics, 60% hyposmics, and 4% normosmic. Repeated-measures analysis showed a significant effect of group ($F = 53.882$; $P < 0.001$) and time ($F = 6.203$; $P = 0.016$), but the group-by-time interaction did not achieve statistical significance ($F = 0.277$; $P = 0.601$).

In patients, UPSIT scores correlated significantly with age at time 1 ($r = -0.469$; $P = 0.018$), and with years of disease duration ($r = -0.434$; $P = 0.030$) and LEDD ($r = -0.463$; $P = 0.020$) at time 2. Qualitatively taking the cut-off of 1.5 standard deviation decline from the baseline scores, 5 controls and 7 patients displayed significant olfactory function loss over time. Patients with olfactory

Table 1
Demographic and clinical characteristics of PD patients and HC at both times.

	PD (n = 25)	HC (n = 24)	Test stats/P-value
Age at baseline, yrs., mean (SD)	61.4 (10.0)	65.3 (8.9)	1.468/0.149[a]
Education, yrs., mean (SD)	12.9 (4.8)	11.2 (4.4)	1.235/0.223[a]
Vocabulary subtest, mean (SD)	49.0 (6.8)	46.8 (7.7)	1.045/0.301[a]
Sex, male, n (%)	14 (56.0)	11 (45.8)	0.506/0.477[b]
Disease duration, yrs., mean (SD)			
Time 1	4.9 (3.5)	NA	NA
Time 2	8.7 (3.4)	NA	NA
Age of onset, yrs., mean (SD)	56.4 (10.3)	NA	NA
UPDRS part III, mean (SD)			
Time 1	14.04 (8.7)	NA	NA
Time 2	16.25 (7.7)	NA	NA
Hoehn & Yahr stage, n 1/1.5/2/2.5/3/4			
Time 1	9/1/12/2/1/0	NA	NA
Time 2	4/0/11/0/10/0	NA	NA
LEDD, mg, mean (SD)			
Time 1	607.8 (433.4)	NA	NA
Time 2	659.2 (371.4)	NA	NA

Abbreviations: HC: healthy controls; LEDD: L-dopa equivalent daily dose; NA: not applicable; PD: Parkinson's disease; UPDRS part III: Unified Parkinson's Disease Rating Scale motor section. Data are presented as mean (SD) or n (%).
[a] Independent t-tests were used for continuous variables when comparing HC with all PD patients.
[b] Pearson's chi-squared tests were used for categorical variables.

Table 2
Olfactory results in PD and HC at both times.

		PD (n = 25)	HC (n = 24)	Test stats/P-value
University of Pennsylvania Smell Identification Test				
Time 1, mean (SD)		20.6 (7.5)	31.3 (3.1)	6.481/<0.001[a]
Time 2, mean (SD)		18.7 (6.4)	30.0 (4.7)	7.036/<0.001[a]
Olfactory status according to UPSIT, n (%)				
Time 1	Anosmics	9 (36.0)	0 (0.0)	
Time 2	Anosmics	12 (48.0)	0 (0.0)	

Abbreviations: HC, healthy controls; PD, Parkinson's disease; UPSIT, *University of Pennsylvania Smell Identification Test.* Data are presented as mean (SD) or n (%).
[a] Independent t-tests were used for continuous variables when comparing HC with all PD patients.

decline did not differ from non-decliners in any clinical or demographic variable.

3.3. Cortical thickness and volumetric changes

Comparison of whole-brain cortical thickness maps showed that both groups had significant progressive cortical thinning in several regions of the posterior cortex. In PD patients, significant cortical thinning was found in the left isthmus of the cingulate gyrus and in the right inferior parietal lobule. In controls, changes over time were seen in the left lingual gyrus and insula, and in the right caudal middle frontal gyrus and lateral occipital regions (Fig. 1). No significant group-by-time interactions were seen between controls and patients.

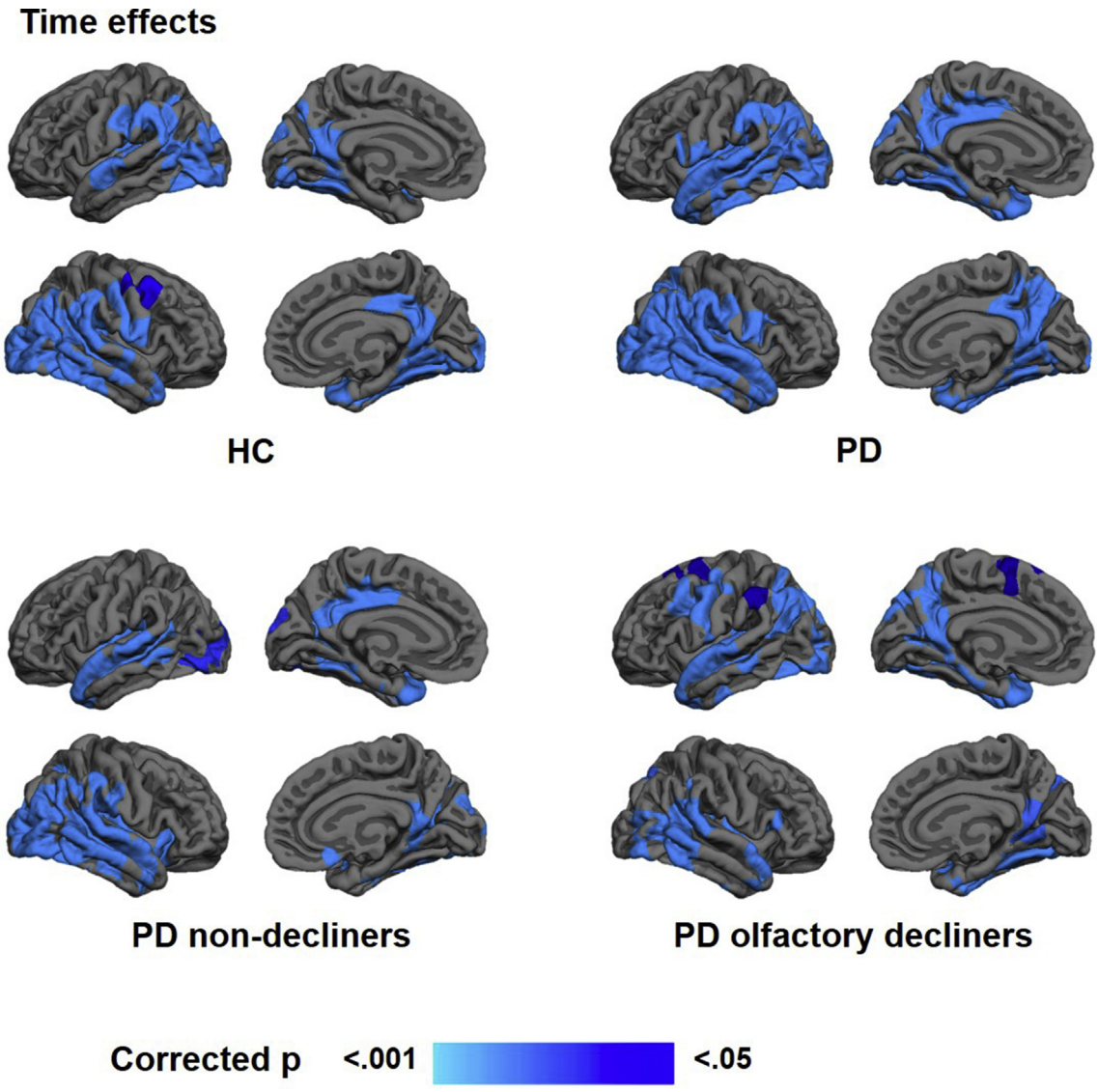

Fig. 1. Abbreviations: HC: healthy controls; PD: Parkinson's disease. Results were obtained using Monte Carlo simulation with 10,000 iterations applied to cortical thickness maps to provide cluster-wise correction for multiple comparisons. Simulation was applied for negative time effects (time 2 < time 1) in each group. Clusters with corrected p < .05 are shown.

The analysis of volumetric changes in the regions of interest of the olfactory system showed that PD patients had greater percentage of volume loss in the right putamen in comparison with HC ($t = 2.676$; $P = 0.010$). Differences remain significant after controlling for general cognitive status, age, and gender ($F = 6.504$; $P = 0.014$).

Correlations between the percentage of change in UPSIT scores and basal ganglia volumes, corrected for multiple comparisons using FDR, showed statistical significance for PD patients in the right thalamus ($P = 0.044$), right caudate ($P = 0.049$), and left putamen ($P = 0.044$) (Fig. 2).

Regarding changes in subcortical volumes over time, PD with olfactory decline had greater right caudate loss in comparison with PD without olfactory decline ($U = 22.000$; $P = 0.012$).

4. Discussion

Our results demonstrate that olfactory impairments progress over time in PD patients, as we detected significant worsening after four years of follow-up. However, the progression of smell impairment was similar to that identified in the control group. These results seem to suggest that aging per se could be responsible for the observed changes in olfactory ability. An alternative explanation could be that atrophy in different brain structures might produce similar clinical changes.

In our study, the prevalence of olfactory deficits as well as the mean scores observed in patients and controls are similar to previous reports using UPSIT with larger samples [1]. Our sample could thus be considered representative of olfactory dysfunctions in PD. We found that the distribution of the degree of impairment in PD patients in the first assessment was 36% anosmics, 60% hyposmics, and 4% normosmic. Regarding the decline in olfactory performance, our results agree with those from a previous longitudinal study performed in a sample of 19 PD patients studied twice with an interval of five years using the "sniffin' sticks"; in that study, however, aging effects could not be excluded because the authors did not include a control group in the design [24]. In the present study, we found a significant effect of time during the four-year follow-up in both patients and controls. The scores obtained in the UPSIT diminished a mean of two points in PD patients, and 1.3 points in HC. Taking the cut-off point of 1.5 standard deviation below the baseline score as indicative of decline, we observed olfactory decline in 7 patients, but also in 5 controls. It is well known that aging per se is associated with olfactory decline; McKinnon et al. (2010), using data collected from 732 subjects, estimated that the decrease in UPSIT scores is 3.2 points for every 10 years of age [33]. Loss of olfactory identification ability is seen from the 5th decade onwards, but is most remarkable between the 7th and 8th decades of life [25]. The correlations between UPSIT scores and disease duration that we and other researchers have observed could reflect both aging effects and the progression of the degenerative process.

In the current four-year longitudinal study, we found evidence of progressive cortical thickness reduction, but this atrophy was similar for patients and controls, and was unrelated to the olfactory loss. From a neuropathological point of view, the severity of abnormal protein aggregates (including alpha-synuclein, hyperphospholylated tau protein, and neurofilament protein) in the olfactory bulb and tract increases significantly in neurodegenerative diseases with increasing neuritic Braak stages and McKeith criteria for Lewy body disease [34]. Odor impairment in PD may be due to defective adult neurogenesis. In animal models, dopaminergic deafferentation may result in impaired precursor cell proliferation in the subventricular zone, which provides new olfactory bulb neurons. It also results in an increased number of dopaminergic neurons in the glomerular cell layer of the olfactory bulb. In PD, the survival of newly generated neurons in the bulb is decreased [35]. Moreover, it has been experimentally demonstrated that dopamine modulates adult neurogenesis in vivo and in vitro and that adult neurogenesis is impaired in individuals with PD [36].

It is thus clear that there is a neuropathological basis for progressive odor impairment. Regarding its anatomical correlates, olfactory impairment in PD has been associated with atrophy of the olfactory bulb [17–19], piriform cortex [21,37], and orbitofrontal cortex [21]. The gray matter correlates of olfactory deficits differ according to the disease stage; in early PD patients, significant correlations are seen in the right piriform cortex, while in moderate and advanced patients the right amygdala is implicated [37]. According to Braak stages [16], the orbitofrontal cortex, a tertiary olfactory structure, is affected relatively early, and prior to posterior parietal regions. Changes in orbitofrontal cortex are therefore expected in early disease stages. Lack of change over the study time in

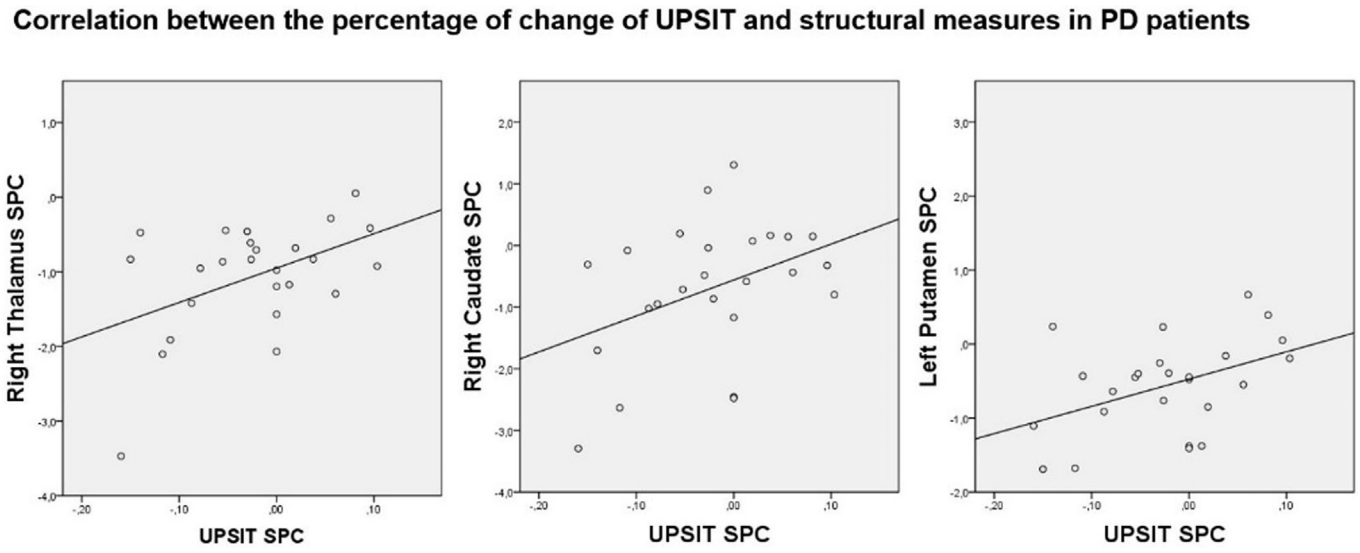

Fig. 2. Significant correlation between the percentages of change in UPSIT scores and subcortical volumes. SPC: symmetrized percentage change.

these structures might be explained by the topographical progression of Lewy-type lesions proposed by the Braak staging. It is possible that further longitudinal studies in *de novo* samples could help identify the relationship between orbital frontal atrophy and loss of odor identification.

In contrast to the lack of cortical correlates of smell loss in PD, we observed significant correlations between the percentage of change in UPSIT scores and the percentage of volume loss in some striatal regions related to the olfactory system. In normal subjects, PET studies showed activation in the thalamus and right caudate during olfactory perception [38]. In fMRI studies, activation was reported in the left putamen [39,40] and caudate [40]. In PD, odor perception activates the bilateral putamen [39], left caudate, and left putamen [40]. Thus, although the striatal nuclei are not classically considered as olfactory structures, they appear to be part of circuitry involved in olfactory perception. Moreover, olfactory performance in PD have been reported to be correlated with gray matter density in the caudate and putamen [41]. However, an alternative interpretation of our results is that striatal atrophy may reflect the rapid disease progression in PD with severe olfactory impairment. In a cross-sectional study, it has been observed that abnormal odor identification was associated with more advanced stages of PD and increased severity of motor symptoms [42]. Similarly, it has been reported that regional mean diffusivity values of the substantia nigra and the olfactory tract correlated significantly with putaminal dopaminergic dysfunction [43].

In conclusion, PD patients and healthy controls matched by age showed a significant similar progressive olfactory loss and a progressive reduction of cortical thickness mainly involving posterior regions, but olfactory loss was associated with basal ganglia volume reductions only in PD.

Disclosures

Authors CU, BS, HCB, AA, AGD, AC, MJM, FV, NB and CJ report no disclosure. YC has received funding, research support and/or honoraria in the last 5 years from Union Chimique Belge (UCB pharma), Lundbeck, Medtronic, Abbvie, Novartis, GSK, Boehringer, Pfizer, Merz, Piramal Imaging and Esteve.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.05.005.

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