Published in final edited form as:

Mov Disord. 2014 August ; 29(9): 1205–1208. doi:10.1002/mds.25829.

Olfactory-related cortical atrophy is associated with olfactory dysfunction in Parkinson's disease

Eun-Young Lee, Ph.D.¹, Paul J. Eslinger, Ph.D.^{1,2,4}, Guangwei Du, M.D., Ph.D.¹, Lan Kong, Ph.D.², Mechelle M. Lewis, Ph.D.^{1,3}, and Xuemei Huang, M.D., Ph.D.^{1,3,4,5,6,*}

¹Department of Neurology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

²Department of Public Health Sciences, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

³Department of Pharmacology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

⁴Department of Radiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

⁵Department of Neurosurgery, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

⁶Department of Kinesiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey PA 17033

Abstract

Background—Olfactory dysfunction is often associated with Parkinson's disease (PD) and can precede characteristic motor symptoms by several years. Olfactory-related cortical atrophy has been reported in PD, although the extent and association between cortical atrophy and olfactory dysfunction have been controversial. The present study examined whether olfactory dysfunction is associated with gray matter (GM) volume in brain regions subserving primary and secondary olfactory processing.

*Corresponding author. Penn State Hershey Medical Center, 500 University Dr., H-037 P.O. Box 850, Hershey, PA 17033-0850. Tel.: 717-531-1803; fax: 717-531-0226. xuemei@psu.edu (X. Huang).

Financial Disclosure: The authors report no conflicts of interest.

Statistical analysis: Performed by Drs. Eun-Young Lee and Lan Kong.

Contributorship:

Eun-Young Lee: Conception and design of the study; data analysis and interpretation; statistical analysis; primary drafting

Paul J. Eslinger: Conception and design of the study; data acquisition, analysis, and interpretation; drafting

Guangwei Du: Data acquisition and interpretation; drafting

Lan Kong: Statistical analysis of the data

Mechelle M. Lewis: Data acquisition and interpretation; administrative support for the study

Xuemei Huang: Conception and design of the study; data acquisition and interpretation; drafting; funding of the study; administration and supervision of the project

Data Sharing

Readers are welcome to contact the corresponding author regarding any additional data analyses.

Methods—High-resolution T1-weighted brain magnetic resonance images were acquired from 40 PD without dementia and 40 matched Controls along with smell identification scores. Brain volumes were compared using voxel-based morphometry (VBM).

Results—Compared to Controls, PD patients sustained greater GM loss localized to bilateral piriform cortex (PC) and orbitofrontal cortex (OFC). Reduced olfactory performance in PD was significantly associated with lower GM volumes in PC and OFC.

Conclusions—Both primary and secondary olfactory cortical atrophy occurred in PD and were associated with olfactory dysfunction.

Keywords

Parkinson's disease; olfaction; MRI; Voxel-based morphometry; olfactory cortex

Introduction

Olfactory dysfunction is one of the earliest signs in Parkinson's disease (PD) and often precedes the characteristic motor symptoms by several years [1], though its exact neural mechanisms still are unclear. Whereas cardinal motor impairments are caused primarily by dopamine depletion in the nigrostriatal pathway, olfactory symptoms seem to be unaffected by dopaminergic treatments, suggesting involvement of other neurotransmitter systems (e.g., cholinergic; [2]) and/or extranigral pathology (e.g., limbic system; [3]). Indeed, Lewy body accumulation in PD has been reported in olfactory-related structures (e.g., olfactory bulb (OB) and piriform cortex (PC); [4]). Furthermore, some recent studies report brain atrophy in regions related to primary olfactory and/or secondary integrative olfactory processing, [e.g., OB, PC, and orbitofrontal cortex (OFC)] in early stage PD [3, 5–6].

Olfactory-related brain atrophy and its association with olfactory dysfunction are, however, controversial. For example, volume loss in OB was positively correlated with olfactory performance in one study [5], but not in the other [7]. Other studies identified cortical gray matter (GM) loss where one linked right PC to olfactory deficit [3] but another failed to detect any association between GM loss and impaired olfaction [6, 8]. The present study examined olfactory-related cortical atrophy in PD and explored its relationship with olfactory dysfunction in a relatively large, early-stage sample.

Methods

Subjects

Forty right-handed PD patients and 40 Controls were matched for age, years of education, gender, and handedness. PD subjects were diagnosed by a movement disorders specialist (XH) according to published criteria [9] and optimally managed medically. All subjects were negative for other neurological disorders. Two subjects with very mild symptoms were drug naïve, but remaining patients were treated with anti-parkinsonian medications [10]. Levodopa equivalent dosage was calculated [11]. Controls had no history of neurologic or psychiatric disorder. All subjects were free of dementia (Mini-Mental Status Examination (MMSE) Score ≥ 26). The Hamilton Depression Rating Scale (HAM-D; [12]) was

completed to assess depression and disease severity was evaluated using the United Parkinson's Disease Rating Scales III (UPDRS) [13] and Hoehn and Yahr scores (H&Y; 14). Thirty-eight PD and 39 Controls completed the University of Pennsylvania Smell Identification Test (UPSIT, range 0–40, with 40 being the best score; [15]) (see Table 1). The study was approved by the Institutional Review Board/Human Subjects Protection Office of the Penn State Hershey Medical Center. Written informed consent was obtained from all subjects.

Magnetic Resonance Imaging acquisition and VBM analysis

High-resolution T1-weighted images were acquired on a Siemens 3-Tesla TimTrio MRI with an 8-channel birdcage type *In vivo* coil with the following parameters: 3D MPRAGE, TR=1540 ms, TE=2.3 ms, voxel spacing 1.0×1.0×1.0 mm, image resolution 256×256 mm², and 176 slices with no gap.

A VBM analysis was carried out using the *FMRIB Software Library* (FSL) tools [16]. First, brain-extracted structural images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Next, GM images were registered to a standard space and averaged to create the study-specific template. Individual GM images then were non-linearly registered to the study-specific template (spatial normalization). The resulting GM images were modulated by multiplying with Jacobian determinants to correct for volume change induced by the nonlinear spatial normalization. Finally, the images were smoothed with an isotropic Gaussian kernel of 9 mm. For the statistical analysis, permutation-based non-parametric testing (5000 permutations) was used with adjustments for depression [17] and total intracranial volume. Based on a priori hypotheses, group differences were considered significant at uncorrected $p < 0.005$ for limbic and paralimbic cortex, including PC and OFC, and at *FWE* (family-wise) corrected $p < 0.05$ for other brain regions.

Correlation Analysis of GM Volume and Olfactory Dysfunction

To explore any correlations between UPSIT scores and olfactory-related primary and secondary cortical GM volume, Spearman's partial correlation analyses were performed separately in both PD and Controls with adjustment for age. For PD, the correlation analysis was controlled additionally for disease duration and H&Y score. We reported raw p -values without correction for multiple comparisons due to the exploratory nature of the analysis.

Results

Demographics (Table 1)

There were no significant group differences in age, MMSE, sex ratio, or education. PD subjects had significantly higher UPDRS III and HAM-D scores. Average disease duration was 3.1 years, with a median of 2 years. Average H&Y stage was 1.8, with 15 subjects being at stage 1, 22 subjects at stage 2, and 3 subjects at stage 3.

Olfactory Function

PD patients scored significantly lower on the UPSIT compared to Controls ($p < 0.0001$) after adjusting for age. PD patients were, on average, hyposmic [mean (SD): 22.55 (6.55)], whereas Controls had normal olfactory function [mean (SD): 34.38 (5.38)].

VBM Analysis (Figure 1: A–C)

PD subjects had reduced volume in bilateral inferior PC (−8, −2, −32; Z-score= 4.28 for left; 20, 10, −36; Z-score= 3.47 for right) and bilateral anterior OFC (−26, 62, −14; Z-score= 3.56 for left; 14, 56, −16; Z-score= 3.93 for right) compared to Controls ($p < 0.005$, uncorrected). For other brain regions, PD patients revealed GM volume reduction in frontal pole/anterior OFC and parieto-occipital regions compared to Controls at *FWE* (family-wise error) corrected $p < 0.05$ (data not reported; see [18] for details).

Correlation Analysis of GM Volume with UPSIT scores (Figure 1: D)

For PD patients, Spearman's partial correlation analyses adjusted for age, disease duration, and H&Y score revealed that right PC [$R = 0.33$, uncorrected $p = 0.028$, *1-tailed*, $N = 38$] and left OFC [$R = 0.37$, uncorrected $p = 0.015$, *1-tailed*, $N = 38$] were positively correlated with UPSIT scores. Left PC and right OFC failed to reach significance [$R = -0.002$, $p = 0.49$ for left PC and $R = 0.21$, $p = 0.11$ for right OFC]. For frontal and parieto-occipital regions where patients showed atrophy, there were no positive correlations between cortical volume and UPSIT scores ($ps > 0.1$) except for the OFC (reported above). There were no correlations between GM volume and UPSIT scores in Controls after controlling for age ($ps > 0.31$).

Discussion

Results revealed that PD patients without dementia display atrophy in cortices subserving olfaction, specifically in inferior PC and anterior OFC. Furthermore, both PC and OFC GM volumes were positively correlated with UPSIT scores in PD, indicating that olfactory dysfunction varied in relationship to olfactory-related cortical atrophy. Interestingly, the association was lateralized and put forward some intriguing possibilities related to the pathophysiology of PD olfactory impairment. To our knowledge, current results comprise the largest study on this topic and is noteworthy for the detection of significant atrophy in regions related to both primary (inferior PC) and secondary integrative (anterior OFC; [19]) olfactory processing. Since bilateral PC and OFC have been reported to be involved in olfactory processing [20–22], the findings of their volume loss in PD are consistent with extranigral cortical involvement in PD-related olfactory dysfunction [4].

The significance of olfactory-related cortical atrophy in PD has been controversial [3, 5–7, 23]. Previous studies have been equivocal regarding the functional implication of olfactory-related cortical atrophy [3, 7]. This controversy may be due partly to differences in specific tests used to assess olfactory function. For example, PC GM loss was associated with olfactory dysfunction measured with the standard Sniffin' Sticks test, which comprises odor threshold, discrimination, and identification components [3]. Unfortunately, this study did not clarify the contribution of each component to the cortical atrophy. A later study [6] examined the relationship between cortical atrophy and odor threshold ability and failed to

show any association. The UPSIT we used mainly assesses odor identification and was found to be associated with olfactory-related GM volume. Together, these findings suggest that some components (e.g., identification) may be more sensitive to GM loss over others (e.g. threshold) and raise the possibility of different neural correlates for each odor processing component.

Our finding of the association of right PC volume with olfactory performance has been described previously [3]. The exact mechanism underlying this lateralization, however, is unclear. Since right PC might be engaged more in judging odor familiarity and the left more in remembering exact odor identities [24], it is possible that odor identification performance in our hyposmic PD subjects relied more on familiarity when presented with UPSIT multiple choices.

The association between left OFC volume and UPSIT performance in PD is novel and intriguing. Left OFC has been implicated in hedonic odor judgment [25], which may contribute to UPSIT performance. Indeed, impaired hedonic odor judgment was associated with reduced smell identification performance in patients with Deficit Syndrome Schizophrenia [26]. It is possible that PD subjects have more difficulty in leveraging the hedonic association of odors to facilitate identification because they are known to experience difficulty in appreciating hedonic cues (e.g., anhedonia; [27]). Thus, we hypothesize that the neural pathway involving hedonic processing (e.g., orbitofrontal-medial PFC-ventral striatum circuit, [28–30]) is compromised in PD, which may have contributed to our findings of the association between UPSIT and left OFC. Future studies that examine the emotional associations to each odor can test this hypothesis.

Lastly, we would like to point out that a small proportion of PD patients may still have normal olfaction [31]. Future studies focusing on this population will be very helpful to clarify the universality of this cortical atrophy.

Acknowledgments

This work was supported by grants NS060722 (XH), and the HMC GCRC (NIH M01RR10732) and GCRC Construction (C06RR016499) Grants. We thank all the participants in the study, as well as their caregivers, and acknowledge the critical support of the study coordinator, Ms. Brittany Jones, and the MRI technical expertise from Mr. Jeffery Vesek.

References

1. Hoyles K, Sharma JC. Olfactory loss as a supporting feature in the diagnosis of Parkinson's disease: a pragmatic approach. *J Neurol*. 2013
2. Bohnen NI, Muller ML, Kotagal V, Koeppe RA, Kilbourn MA, Albin RL, et al. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease. *Brain*. 2010; 133:1747–1754. [PubMed: 20413575]
3. Wattendorf E, Welge-Luessen A, Fiedler K, Bilecen D, Wolfensberger M, Fuhr P, et al. Olfactory impairment predicts brain atrophy in Parkinson's disease. *J Neurosci*. 2009; 29:15410–15413. [PubMed: 20007465]
4. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003; 24:197–211. [PubMed: 12498954]

5. Brodoehl S, Klingner C, Volk GF, Bitter T, Witte OW, Redecker C. Decreased olfactory bulb volume in idiopathic Parkinson's disease detected by 3.0-Tesla magnetic resonance imaging. *Mov Disord.* 2012; 27:1019–1025. [PubMed: 22730050]
6. Wu X, Yu C, Fan F, Zhang K, Zhu C, Wu T, et al. Correlation between progressive changes in piriform cortex and olfactory performance in early Parkinson's disease. *Eur Neurol.* 2011; 66:98–105. [PubMed: 21846992]
7. Mueller A, Abolmaali N, Hakimi A, Gloeckler T, Herting B, Reichmann H, et al. Olfactory bulb volumes in patients with idiopathic Parkinson's disease a pilot study. *J Neural Transm.* 2005; 112:1363–1370. [PubMed: 15711853]
8. Lee JE, Cho KH, Ham JH, Song SK, Sohn YH, Lee PH. Olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord.* 2013
9. Calne D, Snow B, Lee C. Criteria for diagnosing Parkinson's disease. *Ann Neurol.* 1992; 32:S125–S127. [PubMed: 1510370]
10. Clarke CE. Neuroprotection and pharmacotherapy for motor symptoms in Parkinson's disease. *Lancet Neurol.* 2004; 3(8):466–474. [PubMed: 15261607]
11. 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.* 25(15):2649–2653. [PubMed: 21069833]
12. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56. [PubMed: 14399272]
13. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord.* 2008; 23:2129–2170. [PubMed: 19025984]
14. Hoehn MYM. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;427–442. [PubMed: 6067254]
15. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope.* 1984; 94:176–178. [PubMed: 6694486]
16. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage.* 2004; 23:S208–S219. [PubMed: 15501092]
17. Feldmann A, Illes Z, Kosztolanyi P, Illes E, Mike A, Kover F, et al. Morphometric changes of gray matter in Parkinson's disease with depression: A voxel-based morphometry study. *Mov Disord.* 2008; 23(1):42–46. [PubMed: 17973326]
18. Lee E, Sen S, Eslinger PJ, Wagner D, Shaffer ML, et al. Early cortical gray matter loss and cognitive correlates in non-demented Parkinson's patients. *Parkinsonism Relat Disord.* 2013 <http://dx.doi.org/10.1016/j.parkreldis.2013.07.018>.
19. Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani D, Glover G, et al. Dissociated neural representations of intensity and valence in human olfaction. *Nature Neurosci.* 2003; 6:196–202. [PubMed: 12536208]
20. Gottfried JA, Zald DH. On the scent of human olfactory orbitofrontal cortex: meta-analysis and comparison to non-human primates. *Brain Res Rev.* 2005; 50(2):287–304. [PubMed: 16213593]
21. Li W, Luxenberg E, Parrish T, Gottfried JA. Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices. *Neuron.* 2006; 52(6):1097–1108. [PubMed: 17178411]
22. Sobel N, Prabhakaran V, Zhao Z, Desmond JE, Glover GH, Sullivan EV, et al. Time course of odorant-induced activation in the human primary olfactory cortex. *J Neurophysiol.* 2000; 83(1): 537–551. [PubMed: 10634894]
23. Baba T, Kikuchi A, Hirayama K, Nishio Y, Hosokai Y, Kanno S, et al. Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. *Brain.* 2012; 135:161–169. [PubMed: 22287381]

24. Plailly J, Bensafi M, Pachot-Clouard M, Delon-Martin C, Kareken DA, Rouby C, et al. Involvement of right piriform cortex in olfactory familiarity judgments. *Neuroimage*. 2005; 24:1032–1041. [PubMed: 15670680]
25. Royet J-P, Plailly J, Delon-Martin C, Kareken DA, Segebarth C. fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. *Neuroimage*. 2003; 20:713–728. [PubMed: 14568446]
26. Strauss GP, Allen DN, Ross SA, Duke LA, Schwartz J. Olfactory hedonic judgment in patients with deficit syndrome schizophrenia. *Schizophr Bull*. 2010; 36(4):860–868.
27. Assogna F, Cravello L, Caltagirone C, Spalletta G. Anhedonia in Parkinson's disease: a systematic review of the literature. *Mov Disord*. 2011; 26:1825–1834. [PubMed: 21661052]
28. Haber S, Kunishio K, Mizobuchi M, Lynd-Balta E. The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci*. 1995; 15(7):4851–4867. [PubMed: 7623116]
29. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006; 16(7):916–928. [PubMed: 16207933]
30. Schultz W, Tremblay Lo, Hollerman JR. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb Cortex*. 2000; 10(3):272–283. [PubMed: 10731222]
31. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*. 1988; 38:1237–1244. [PubMed: 3399075]

Figure 1.

VBM results contrasting PD < Controls indicate GM volume loss in PD subjects in (A) Right inferior piriform cortex (A-1: axial view and A-2: coronal view), B) Left inferior piriform cortex (B-1: axial view and B-2: coronal view); (C) Bilateral anterior orbitofrontal cortex (C-1: axial view and C-2: coronal view); (D) Scatter plots of gray matter volume with UPSIT scores for both PD and Controls: PD GM volume (ml) in the right inferior piriform cortex (D-1) and left anterior orbitofrontal cortex (D-2) correlated with UPSIT scores

Table 1

Demographic information and general characteristics of the study subjects

	Controls (n=40)	PD (n=40)	P - value
Age (years)	58 ± 6	59 ± 7	0.85
Sex (male/female) [†]	19/21	21/19	0.82
Education (years)	16 ± 3	15 ± 3	0.41
MMSE score	29.6 ± 0.8	29.4 ± 1	0.32
Disease duration (yrs.)	0	3.1 ± 3.2	n.a.
Levodopa Equivalent Dose (mg/day)	0	322.1 ± 244.4	n.a.
UPDRS-III	0.9 ± 2.1	17.7 ± 10.7	<0.0001*
Hoehn & Yahr stage	n.a.	1.8 ± 0.7	n.a.
Hamilton Depression Score	3.8 ± 2.1	7.4 ± 3.9	<0.0001*

Demographic information is shown as mean ± standard deviation. *P-values* were derived from a simple one-way analysis of variance comparing the two groups, except for † that was derived using Fisher's Exact test.

* All comparisons were considered statistically significant at $p < 0.05$.

[MMSE = Mini Mental Status Examination; UPDRS-III = Unified Parkinson's Disease Rating Scale III.]