

NEUROLOGICAL BULLETIN

FEATURING ARTICLES BY TRAINEES IN NEUROLOGY & NEUROSCIENCE

DBS-implanted Parkinson's Disease Patients Show Better Olfaction Than Those Treated Medically

Mary Linton Peters, Paula Ravin, Peter Novak,
Anthony M. Burrows, Joan Swearer, Jean King,
Sathish Kumar Dundamadappa, and Julie G. Pilitsis

Department of Surgery, Division of Neurosurgery
University of Massachusetts Medical School, Worcester, MA

Abstract

Dysosmia in PD (Parkinson's Disease) may result from changes in the olfactory apparatus or in structures involved in olfactory perception. Previous work^{1,2} has suggested that deep brain stimulation (DBS) patients have improved odor discrimination in stimulation-on/medication-off state in comparison to their own scores in a stimulation-off/medication-off state. What remains unclear is whether it is the ON state itself or an effect of stimulation that leads to improved olfaction. In this study we evaluate dysosmia in two PD cohorts in the ON state, those treated with medication alone and those treated with medication and DBS.

A prospective study geared at improving predictive value of olfactory testing with a battery of psychological tests enrolled 45 PD patients and 44 controls. Of the PD patients, 9 had bilateral STN (subthalamic nucleus) DBS and 36 were medically treated. Subset analysis of PD patients with and without DBS placement revealed no difference in apathy or depression. DBS patients had better olfaction on UPSIT (Univ of Pennsylvania Smell Identification Test) ($p < 0.05$). No difference was noted in disease severity, gender, smoking status, medication dosing, use of dopamine agonists, or maximal olfactory sulcus depth on MRI. DBS patients were significantly younger, however inter-group differences in UPSIT scores exceeded those seen in our control cohort with similar ages.

This study provides further data that DBS patients have improved olfaction. It also provides preliminary evidence that DBS with medication improves dysosmia to a greater extent than medication alone. This may result from indirect stimulation of olfactory processing centers or changes in olfactory circuitry metabolism.

Correspondence to Julie Pilitsis: julie.pilitsis@umassmemorial.org

Keywords: Parkinson's Disease, olfaction, deep brain stimulation

Introduction

Deep brain stimulation (DBS) is used in the treatment of Parkinson's Disease (PD), and has been shown to improve motor symptoms to a greater extent than optimal medical therapy in selected patients.³ In addition to motor symptoms, PD is characterized by a set of autonomic, cognitive, and emotional non-motor symptoms. Olfaction is lost early in the disease process of idiopathic PD. A 2006 practice parameter statement regarding the diagnosis of PD concluded that olfaction testing could help to differentiate new-onset idiopathic PD from other Parkinsonian syndromes.^{4,5}

Our study was designed to test several surveys of non-motor symptoms of PD for their potential as diagnostics in an office-based setting. The University of Pennsylvania Smell Identification Test (UPSIT)⁶ differs from other olfactory tests because of its ability to be self-administered and its everyday relevance. It is a 40-question forced choice scratch-and-sniff test in which fewer than 18 correct answers indicates anosmia. Among the 45 PD patients recruited for the study, nine had received bilateral subthalamic nucleus (STN) deep brain stimulation. This analysis investigates the difference in non-motor symptoms, particularly olfaction, between patients treated medically and those treated with medical therapy combined with DBS.

Methods

After obtaining permission from the Institutional Review Board, subjects were recruited from the neurology, surgery, and otolaryngology clinics at U Mass University Hospital and provided written informed consent. All subjects were free of cognitive impairment and of ongoing respiratory infections. Patients were determined by their treating neurologist to have a diagnosis of idiopathic PD⁷ of Hoehn and Yahr stage 1-3, and to be free of confounding psychiatric disorders. Controls were determined by their treating physician to be free of PD and psychiatric disorders. Within the patient group, 9 subjects had bilateral DBS placement in the STN.

Subjects completed four surveys: UPSIT,⁶ the Beck Depression Inventory (BDI),⁸ the Apathy Evaluation Scale – Self-administered version (AES),⁹ and the UK Parkinson's Disease Society non-motor symptoms assessment questionnaire (PDS).¹⁰ All surveys were self-administered in writing following written instructions. A research assistant was available to answer questions if necessary.

Olfaction re-testing was performed with 5 of the 9 DBS patients in a stimulator-off/medication-on state. During these tests, the DBS stimulators were off for a minimum of 30 minutes. Medication use was not varied.

Comparisons were analyzed with chi-square,

Table 1	DBS (n=9)	Medically treated (n=36)	p-value
Age	61 (55-68)	71 (53-88)	0.01
Hoehn and Yahr Stage	2.83 (2-3)	2.44 (1-3)	0.07
Age at Disease Onset*	46	63	0.003
Duration of Disease*	15	8	0.002
% Female	33 %	22 %	0.49
Current Smokers	0 %	6 %	
Past Smokers	22 %	31 %	

* Disease onset information is not available for 9 study participants

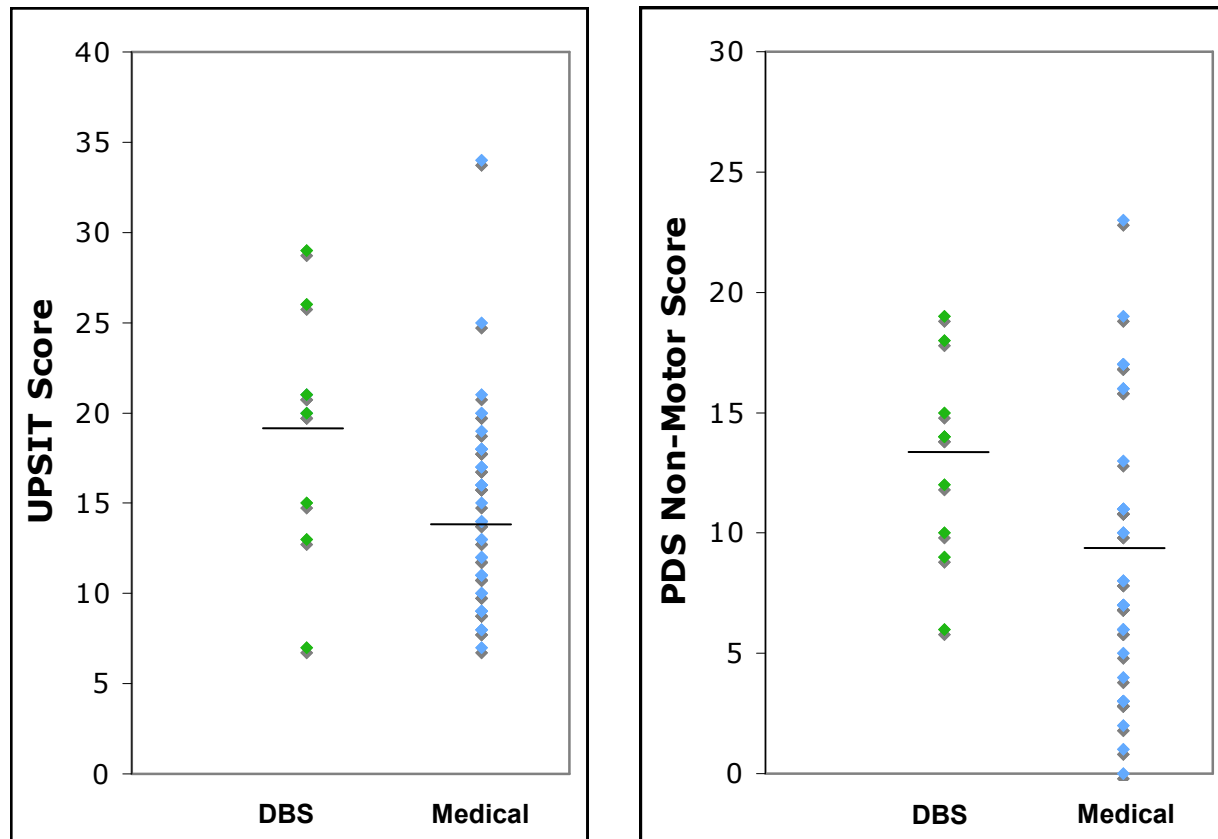


Figure 1 (on left): Olfaction in DBS and Medically-Treated PD Patients

Figure 2 (on right): PDS Score in DBS and Medically-Treated PD Patients

t-test, logistic regression, and linear regression calculations performed in Microsoft Excel (Microsoft Corp, version 11) and STATA (StataCorp, version 10); $p < 0.05$ was considered statistically significant.

Results

All four of the tested surveys were shown to be significantly better in the age-matched control group without PD than the PD disease group. Olfaction in particular was shown to be significantly poorer in the PD group, and to have sufficient predictive value to be useful as a diagnostic tool (results not shown).

Within the PD group, 9 patients had received bilateral STN DBS (**Table 1**). The DBS patients were younger than the medically treated group (average age 61 vs. 71), and had more severe disease (Hoehn and Yahr stage 2.83 vs. 2.44). The DBS patients also demonstrated an earlier age of disease onset and longer disease duration.

The DBS group showed significantly improved olfaction (mean 19.1 ± 6.7) compared to the medically-treated group (mean 14.5 ± 5.5 , $p < 0.05$) (**Figure 1**). In contrast, the DBS group showed more general non-motor symptoms (mean 13.0 ± 4.2) compared to the medically-treated group (mean 8.9 ± 5.7 , $p =$

Table 2	DBS subset (n=8)	Medically treated subset (n=11)
Age	62 (55-68)	63 (53-68)
Hoehn and Yahr Stage	2.94 (2.5-3)	2.77 (2.5-3)
% Female	38 %	27 %

0.05) (**Figure 2**). The other two surveys, of depression and apathy, were not significantly different between the two groups. Logistic regression yielded olfaction odds ratio of 1.13 (1.00-1.29, $p = 0.04$) and a non-motor odds ratio of 1.14 (0.99 – 1.32, $p = 0.05$).

Further analysis was conducted to assess the impact of demographic variability on olfactory and non-motor systems testing. Linear regression conducted on the results using both age and gender as dependent variables yielded an r-squared effect size of 15%.

We created age and gender matched groups by selecting only those patients between the ages of 50 and 69 with Hoehn and Yahr scores of 2.5 or above (**Table 2**). In these similar groups, the differences in olfaction and non-motor symptoms remained significant (olfaction $p < 0.05$, non-motor $p = 0.05$).

We then investigated the role of stimulation in olfactory processing by retesting 5 of the 9 DBS patients in a stimulator-off/medication-on state. As a group, their olfaction was the same.

Conclusions

There are a number of reasons why olfaction may be different between the DBS/medication and medication alone cohorts. In

part, the difference between our two groups may be a result of changes in metabolism either in the striatum, other basal ganglia areas, or potentially in other regions of the brain. Changes in metabolism in the striatum and thalamus in PD is complex and involves alterations in receptor availability as well as neurotransmitter processing.¹¹ Studies in rats with 6-hydroxydopamine lesioning have shown a number of changes in metabolism with prolonged high frequency stimulation (HFS), including normalization of COX levels in the substantia nigra with HFS.¹² In the same model, Cytochrome oxidase I mRNA levels in cortical regions have also shown to normalize following HFS.¹³ HFS has thus been implicated in altered transcription and signaling in both cortex and basal ganglia. It is plausible that long term HFS stimulation could similarly affect regions associated with olfaction including the amygdala and olfactory nucleus.

Alternatively, the improvement in olfaction with DBS may be due to indirect stimulation of olfaction processing centers. A recent study using 18-fluorodeoxyglucose PET in PD patients with DBS has shown that normalized resting cerebral metabolic rates of glucose increase with DBS around the electrode, as well as in the center of the STN and the globus pallidus.¹⁴ Furthermore, a recent study in a rat model of PD suggests that cor-

tical electrical activity can be altered by STN HFS,¹⁵ providing evidence that DBS affects brain circuitry locally and globally. Thus, stimulation may potentially have an effect on thalamocortical circuits involved in processing olfaction signals. Olfaction in a subset of the DBS cohort was the same in the stimulation-off/medication-on state as the stimulation-on/medication-on state. This may suggest that olfactory circuit stimulation has a longer response time than thirty minutes. Prior studies have suggested that differences observed in olfaction may be related to the cognitive processing of olfaction as opposed to the physical detection of odors.^{1,2}

Finally, the possibility remains that these differences may reflect an epiphenomenon. This study is limited in that it is a small sample with confounding variables. We have attempted to investigate several of these potential confounding factors. First we examined the role of dopaminergic therapy. Previous studies have shown that the use of dopamine agonists has not been shown to correlate to olfaction.¹⁶ We confirmed this result in our subset. In this study, the DBS group did have a higher average use of dopamine agonists, however most of this difference was due to a single outlier with very significant dosing. The remainder of the group is comparable to those treated solely with medical therapy. The DBS group had an earlier disease onset, which may indicate a genetic component to their disease state. There is evidence that young-onset PD patients display similar non-motor symptoms to later-onset patients but have worsened olfaction. Parkin gene mutation associated disease demonstrates fewer non-motor symptoms, including olfaction.¹⁷ As our DBS group showed increased non-motor symptoms in the context of improved olfaction, this does not seem consistent with either early-onset disease or parkin gene-associated disease.

Our study is inherently limited by its small size. The DBS group is smaller, and there are demographic differences in age and gender. Olfaction is known to degrade with age, and the DBS group is younger than the medically-treated group.¹⁸ Olfaction is also known to differ by gender, as women typically have increased UPSIT scores.¹⁸ We attempted to address this difference both through linear regression analysis and creation of an age and gender matched subset, but neither approach excludes the possibility of an underlying confounding factor. In addition, our study population exhibited a broad range of disease duration, which could be linked to severity of both motor and non-motor symptoms.

In conclusion, we believe that this study provides preliminary evidence that patients with DBS have better olfaction than patients treated medically. This stands in contrast to other non-motor symptoms that are worse in the DBS patients.

References

1. Guo X, Gao G, Wang X, et al. Effects of bilateral deep brain stimulation of the subthalamic nucleus on olfactory function in Parkinson's disease patients. *Stereotact Funct Neurosurg* 2008;86:237-244.
2. Hummel T, Jahnke U, Sommer U, Reichmann H, Müller A. Olfactory function in patients with idiopathic Parkinson's disease: effects of deep brain stimulation in the subthalamic nucleus. *J Neural Transm* 2005;112:669-676.
3. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301:63-73.
4. Suchowersky O, Reich S, Perlmutter J,

- Zesiewicz T, Gronseth G, Weiner WJ. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:968-975.
5. McKinnon JH, Demaerschalk BM, Caviness JN, Wellik KE, Adler CH, Wingerchuk DM. Sniffing out Parkinson disease: can olfactory testing differentiate parkinsonian disorders? *Neurologist* 2007;13:382-385.
 6. 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.
 7. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33-39.
 8. Beck AT. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-71.
 9. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143-162.
 10. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multi-center pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: The NMSQuest study. *Mov Disord* 2006;21:916-923.
 11. Smith Y, Villalba R. Striatal and extrastriatal dopamine in the basal ganglia: An overview of its anatomical organization in normal and Parkinsonian brains. *Mov Disord* 2008;23:S534-S547.
 12. Vlamings R, Visser-Vandewalle V, Kozan R, Kaplan S, Steinbusch HW, Temel Y. Bilateral high frequency stimulation of the subthalamic nucleus normalizes COX activity in the substantia nigra of Parkinsonian rats. *Brain Res* 2009;1288:143-148.
 13. Oueslati A, Sgambato-Faure V, Melon C, et al. High frequency stimulation of the subthalamic nucleus potentiates L-DOPA-induced neurochemical changes in the striatum in a rat model of Parkinson's Disease. *J Neurosci* 2007;27:2377-2386.
 14. Hilker R, Voges J, Weber T, et al. STN-DBS activates the target area in Parkinson disease: an FDG-PET study. *Neurology* 2008;71:708-713.
 15. Lehmkuhle MJ, Bhangoo SS, Kipke DR. The electrocorticogram signal can be modulated with deep brain stimulation of the subthalamic nucleus in the hemiparkinsonian rat. *J Neurophysiol* 2009;102:1811-1820.
 16. Simuni T, Lyons KE, Pahwa R, et al. Treatment of early Parkinson's disease. Part 2. *Eur Neurol* 2009;61:206-215.
 17. Kägi G, Klein C, Wood NW, et al. Nonmotor symptoms in Parkinson gene-related parkinsonism. *Mov Disord* 2010;25:1279-1284.
 18. Ship JA, Weiffenbach JM. Age, gender, medical treatment, and medication effects on smell identification. *J Gerontol* 1993;48:M26-32.

Disclosure: the authors report no conflicts of interest.

Acknowledgement: thanks to the Neurology, Neurosurgery, and Otolaryngology clinics at U Mass Memorial for their assistance with this project.

Supported in part by the Worcester Biomedical Research Foundation (to J.P.) and by the Clinical and Translational Research Pathway of the University of Massachusetts Medical School (to M.P.)

All content in Neurological Bulletin, unless otherwise noted, is licensed under a Creative Commons Attribution-Noncommercial-Share Alike License <http://creativecommons.org/licenses/by-nc-sa/3.0/> (ISSN 1942-4043)