Effects of Bilateral Deep Brain Stimulation of the Subthalamic Nucleus on Olfactory Function in Parkinson's Disease Patients

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Key Words

Parkinson's disease • Deep brain stimulation • Olfaction • Identification threshold • Detection threshold • Subthalamic nucleus

Abstract

Objective: The goal of the present study was to evaluate the effects of bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on olfaction in patients with Parkinson's disease (PD). **Methods:** 15 patients suffering from sporadic PD-related dysosmia were implanted with bilateral electrodes aimed at the STN. One week before the surgery, odor detection threshold (DT) and identification threshold (IT) were evaluated in all patients using the 'five odor olfactory detection arrays' in both medication-off and medication-on conditions. 15 healthy age-matched controls also received the same olfactory evaluation. Patient evaluations were repeated at 6 and 12 months postoperatively in a medication-off/stimulator-on or medication-off/stimulator-off condition. Odor DT and IT scores were compared pre- and postoperatively, as well as between the medication-off/stimulator-on or -off conditions. **Results:** The motor symptoms of all 15 PD patients, including rigidity, tremor, bradykinesia, postural instability, and gait were significantly improved after stimulator implantation. The UPDRS motor

(UPDRS III) scores decreased significantly in the medication-off/stimulator-on condition ($p < 0.01$). The odor DT and IT scores of PD patients were higher than those of healthy controls ($p < 0.01$). In the medication-off/stimulator-off condition, there was no significant difference in the odor DT and IT scores in PD patients pre- vs. postoperatively ($p > 0.05$). Notably, there were no significant alterations to DT scores in the stimulator-on and -off conditions at the 6- and 12-month follow-up ($p > 0.05$), whereas IT scores were significantly improved in the stimulation-on relative to the stimulation-off condition at the 6- and 12-month follow-up. **Conclusions:** STN DBS can significantly improve olfactory cognitive function in PD patients. The possible mechanisms include an improvement in striatal metabolism and neuronal activity in the orbitofrontal cortex mediated by STN DBS, as well as increased glucose metabolism in the striatum, midbrain, cingulate gyrus, and motor and higher-order somatosensory association cortices.

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Introduction

The clinical manifestations of Parkinson's disease (PD) include not only motor dysfunction, such as rigidity, tremor, bradykinesia, and postural and gait disturbances,

but also psychiatric symptoms, including depression, anxiety, sleep disturbances, drug-induced psychosis, and somatosensory disturbances, particularly olfactory deficits. Studies have demonstrated that olfactory dysfunction appears as an early symptom in PD, often before the appearance of motor symptoms [1–7]. Characteristics of olfactory dysfunction include increases in odor detection threshold (DT) and identification threshold (IT), decreases in odor recognition, prolonged latency of olfactory-evoked potential [6], and even anosmia.

Studies have demonstrated that the neuropathological staging of PD can explain the pathogenesis underlying olfactory dysfunction in PD [8, 9]. The theory suggests that the olfactory bulb (OB) and the anterior olfactory nucleus (AON) are adversely affected by the presence of Lewy bodies (LBs) in stage 1. Kim et al. [7] confirmed that a loss of olfactory function precedes the development of motor symptoms because there is no correlation between olfactory deficits and the depth of olfactory sulcus in PD. Lee et al. [10] suggested that the olfactory system represents one of the induction sites for neuropathological processes in PD. The above-mentioned pathological alterations to olfactory pathways or dysfunction of the higher-order processing of olfactory information may underlie olfactory dysfunction [11, 12]. In recent years, subthalamic nucleus (STN) deep brain stimulation (DBS) has become a widely accepted therapy for the long-term treatment of PD [13–18]. However, studies evaluating the efficacy of STN DBS have focused primarily on the improvement of motor symptoms and less on the amelioration of olfactory dysfunction. Olfactory systems play a highly integrated and important role in daily functioning: not only does the olfactory system function to warn of noxious stimuli, it also contributes to various learning and memory processes [19, 20].

The role of DA in the olfactory deficits in PD remains unclear. Research by Doty and colleagues [21–23] found that DA replacement therapy failed to improve olfactory function in PD patients. This may be due to the relative number of dopaminergic neurons: previous studies report a notable increase in DA neurons in the human OB in PD relative to age- and gender-matched controls [4], and DA is known to inhibit excitatory neurotransmission in the OB [24]. Olfactory dysfunction in PD is not dependent on a DA deficiency by an apomorphine test [23]. Transection of the nigrostriatal pathway in the rat increases DA neuron neurogenesis in the OB [25]. By contrast, Ross et al. [26] suggested that reduced levels of DA may underlie the olfactory deficits in PD. The mechanism underlying STN DBS effects in PD is completely

different from that of medication. Therefore, it remains unknown whether this intervention can rescue deficits in olfaction, in addition to its benefits for movement.

A widely-used test of olfactory function in neurodegenerative disease is the University of Pennsylvania Smell Identification Test (UPSIT). There are several versions of this task that include familiar odors for different countries, although there is not yet a Chinese edition, and Chinese populations are generally unfamiliar with the odors on the UPSIT. This may influence the accuracy of olfactory test. Therefore, in the present study, the odor DT and IT were determined by using ‘five odors olfactory detection arrays’ provided by the Chinese Academy of Sciences. The five kinds of odors are acid (acetic acid), amylacetate (banana smell), mint (cooling oil), flower perfume, and osmyl (methyldole), respectively, which are easily identified and could reflect olfactory function more effectively because Chinese people are very familiar with these odors.

Patients and Methods

Subjects

Fifteen consecutive PD patients who underwent bilateral STN DBS were included in the study. The PD subjects included 9 men and 6 women with a mean age of 61.1 ± 7.8 years (range 42–71), a mean disease duration of 11.3 ± 2.9 years (range 6–16) and a mean educational level of 8.9 ± 3.2 years (range 3–14). Six patients complained of decreased olfactory sensitivity (group 1, $n = 6$), and 9 patients were unaware of change in olfaction before testing (group 2, $n = 9$). There were no cases of anosmia. The characteristics of the patients are detailed in table 1. 15 healthy volunteers from the outpatient clinic were included as age-, sex-, and education-matched control. The control group included 8 men and 7 women with a mean age of 62.9 ± 5.4 years (range 46–69), and a mean educational level of 8.9 ± 4.1 years (range 4–15). There were no statistical group differences for age, sex, or educational level ($p > 0.05$). All patients were diagnosed with PD by a neurologist, with at least two of the three cardinal signs (tremor, rigidity and bradykinesia), good initial response to levodopa treatment, but long-term treatment side effects. Patients with Parkinson's plus syndromes, dementia, psychosis, nasal cavity disease or rhinosinusopathia, alcoholism, or a recent (within 3 weeks of study) upper respiratory tract infection were excluded. All patients gave written informed consent according to the Declaration of Helsinki, and the study was approved by the local ethics committee.

Surgical Procedures

A Cosman-Roberts-Wells (Radionics, Inc., Burlington, Mass., USA) stereotactic head ring was placed under local anesthesia. A CT scan of the head was performed with the gantry angled to approximate the anterior commissure-posterior commissure (AC-PC) plane. Imaging location was performed by spiral CT thin-slice scanning (32 slices, 3 mm thickness, 1.5 mm interval) from

Table 1. Preoperative subject characteristics

Patient/ sex	Age years	Duration years	Education years	Baseline scores medication-off/on				
				UPDRS III	UPDRS II	H-Y	DT	IT
1/M	52	7	14	60/14	36/20	4/2	1.8/1.4	3/2.6
2/F	42	12	9	55/16	30/13	3/2	1.4/1.2	2.2/2.6
3/M	67	13	13	54/22	28/11	4/2	1.8/1.6	2.8/2.6
4/F	65	10	12	49/22	27/10	3/2	2.4/2.6	3/2.8
5/F	60	9	7	43/13	23/7	3/2	1.4/1.6	2.2/2.4
6/M	54	6	12	42/7	19/5	3/2	2/2.2	3/3
7/M	70	15	6	66/21	41/22	4/3	1.4/1.2	2.2/2.6
8/F	69	14	7	49/11	27/11	4/3	2/1.6	2.8/2.6
9/M	63	11	3	44/10	23/8	3/2	0.8/0.8	1.6/1.8
10/M	60	10	5	42/19	20/6	3/2	1.6/1.6	2.8/2.6
11/M	56	11	11	39/15	18/8	3/2	1.4/1.6	2/1.6
12/F	61	8	9	34/8	19/6	3/2	1.8/2	2.8/2.6
13/M	71	16	7	68/23	44/22	4/3	1.2/1.4	1.6/1.8
14/M	67	14	11	52/23	29/12	4/3	1.4/1.2	2.2/2
15/F	59	13	8	50/21	28/9	4/3	2/1.8	3/2.8
Mean	61.1	11.3	8.9	49.8/16.3	27.5/11.3	3.5/2.3	1.63/1.58	2.48/2.43
SD	7.8	2.9	3.2	9.7/5.7	7.9/5.7	0.5/0.5	0.39/0.45	0.51/0.42

the base of the sella turcica to the body of the lateral ventricle. The images from the CT were downloaded into the surgical planning system and the software reformatted the image, compensating for pitch, yaw, and roll. The coordinates for the STN were as follows: 4–7 mm below the AC-PC plane, 11–13 mm lateral to the median line, 3–4 mm posterior to the midpoint (MP). A burr hole was created 2.5–3 cm from the midline, anterior to the coronal suture on each side. Microelectrode recording and stimulation techniques were used to further refine the target location. Once an optimal position was selected, macrostimulation was performed and if no side effects were demonstrated, the DBS electrode (model 3387 or model 3389; Medtronic, Inc., Minneapolis, Minn., USA) was implanted and secured at the burr hole site, an extension (Lead 7482-51) was attached to the DBS electrode. Intraoperatively, the patient has a skull X-rays performed for confirmation of electrode placement. Stimulation was again used to confirm there were no side effects. The patients were then placed under general anesthesia and the implantable pulse generators (Kinetra 7428, Medtronic, Inc.) were implanted in a subclavicular, subcutaneous pocket. The implantable pulse generators were programmed 4–6 weeks after the procedure in the medication-off state. The stimulation parameters for DBS were: stimulation frequency (125–185 Hz), stimulation pulse width (60–90 μ s), and stimulation voltage (0.8–3.4 V).

Experimental Protocol

Preoperative UPDRS II (activities of daily living, ADL) scores were assessed for all PD subjects. Preoperatively, the UPDRS II scores were 27.5 ± 7.9 in the medication-off states and 11.3 ± 5.7 in the medication-on states. Hoehn & Yahr staging ranged from 2.5 to 4 in the medication-off states and from 1.5 to 3 in the medication-on states (table 1).

Olfactory Tests

The odor DT and IT were determined using the ‘five odor olfactory detection arrays’ provided by the Chinese Academy of Sciences. The five odors in the olfactory detection arrays included: (a) acid (acetic acid); (b) amylacetate (banana smell); (c) mint (cooling oil); (d) flower perfume, and (e) osmyl (methylindole). Each odor had six grades of concentration, and odor concentrations from high to low, one by one, were diluted 10-fold. The logarithm of the corresponding concentrations of odor was the score of olfactometry, recording 3, 2, 1, 0, –1, –2, respectively. All olfactory measurements were performed in a quiet, well-ventilated room. For testing, an odor was selected at random and tested from the lowest (–2) to the highest concentration (3). The subject was initially asked whether there was odor. When the subject could answer that there was odor but could not exactly identify it, the corresponding score for the concentration was recorded as the DT for this odor and the test was continued until the subject could exactly identify the odor and the IT was recorded. The remaining odors were then tested in turn. The total DT and IT of subjects were calculated according to the mean corresponding DT or IT value for the 5 odors, namely $[(A + B + C + D + E)/5]$. In order to avoid olfactory tolerance, intermission of smelling each odor was not less than 45 s.

Each PD subject was tested 6 times, including 1 week before the surgery, in both medication-off and medication-on conditions (baseline); in the stimulator-on and stimulator-off condition with medication-off at both 6 and 12 months postsurgery. Control subjects were only tested once.

Statistical Analyses

Data were analyzed using SPSS version 11.0 software (SPSS, Inc., Chicago, Ill., USA). Pre- and postoperative UPDRS motor

Table 2. Clinical scores pre- and postsurgery

	Presurgery			Postsurgery off drug					
				6 months			12 months		
	off drug	on drug	p value	off stim	on stim	p value	off stim	on stim	p value
UPDRS III	49.8 ± 9.7	16.3 ± 5.7	t = 16.867 p = 0.000	50.6 ± 9.2	26.6 ± 7.1	t = 17.889 p = 0.000	51.2 ± 10.3	28.1 ± 8.5	t = 14.819 p = 0.000
UPDRS II	27.5 ± 7.9	11.3 ± 5.7	t = 22.118 p = 0.000	28.1 ± 8.2	18.9 ± 6.4	t = 14.294 p = 0.000	28.9 ± 8.4	18.4 ± 6.2	t = 13.979 p = 0.000
DT	1.63 ± 0.39	1.58 ± 0.45	t = 0.676 p = 0.510	1.68 ± 0.43	1.65 ± 0.35	t = 0.695 p = 0.499	1.73 ± 0.40	1.71 ± 0.36	t = 1.000 p = 0.334
IT	2.48 ± 0.51	2.43 ± 0.42	t = 0.774 p = 0.452	2.44 ± 0.47	2.20 ± 0.42	t = 2.449 p = 0.028	2.52 ± 0.38	2.28 ± 0.31	t = 2.553 p = 0.023

p value: on drug versus off drug or on stimulation versus off stimulation.

(III) scores, UPDRS ADL (II) scores, and DT and IT scores are expressed as mean ± SD. These data were analyzed with paired t tests. Pearson's correlations and Spearman's correlations were used to establish relationships between study variables. A p value <0.05 was considered significant.

Results

Effect of Surgery

Postoperatively in the medication-off/stimulator-on condition, UPDRS II and III scores were significantly improved at both 6 months (decreased by 31.3 and 46.5%, respectively; from 27.5 ± 7.9 to 18.9 ± 6.4 and from 49.8 ± 9.7 to 26.6 ± 7.1, respectively) and 12 months (decreased by 33.1 and 42.0%, respectively; from 27.5 ± 7.9 to 18.4 ± 6.2 and 49.8 ± 9.7 to 28.9 ± 8.4, respectively) relative to the presurgery medication-off condition ($p < 0.01$). We also observed significant improvements in tremor, rigidity, and bradykinesia (table 2).

Olfactory Tests

In the medication-off condition before operation, the odor DT for group 1 ($n = 6$) and group 2 ($n = 9$) were 1.80 ± 0.44 and 1.51 ± 0.35 ($t = 1.355$, $p = 0.208$), respectively. The odor IT for group 1 and group 2 were 2.63 ± 0.60 and 2.38 ± 0.44 ($t = 0.896$, $p = 0.395$), respectively. The mean DT and IT scores for group 1 were higher than those of group 2. These findings suggested that the olfactory dysfunction for group 1 was more serious than that for group 2, although the difference was not statistically significant.

When investigating the entire cohort of patients ($n = 15$), the odor DT and IT of PD subjects were 1.58 ± 0.45 and 2.43 ± 0.42, respectively, for the medication-on condition, and 1.63 ± 0.39 and 2.48 ± 0.51, respectively, for the medication-off condition before operation; there was no significant difference between medicated and non-medicated conditions ($p > 0.05$). The odor DT and IT of the healthy control group were 0.41 ± 0.38 and 1.35 ± 0.26, respectively, which were significantly lower than that of the PD group ($p < 0.01$). Therefore, the PD patients in the present study exhibited symptoms of olfactory hypofunction.

The odor DT and IT in the medication-off/stimulator-on and -off conditions were 1.65 ± 0.35, 2.20 ± 0.42 and 1.68 ± 0.43, 2.44 ± 0.47, respectively at 6 months and 1.71 ± 0.36, 2.28 ± 0.31 and 1.73 ± 0.40, 2.52 ± 0.38, respectively at 12 months postoperation (table 2). Postsurgically there were no significant differences in the odor DT scores in the medication-off/stimulator-on condition compared to medication-off/stimulator-off condition at 6 or 12 months. However, the odor IT scores in the stimulator-on condition improved (by 9.8 and 9.5%, respectively) significantly relative to the stimulator-off condition (fig. 1a). Postsurgically there were no significant changes in the odor DT or IT scores in the stimulator-off condition relative to presurgical scores ($p > 0.05$). Results from all tests are shown in table 2.

When compared with presurgical levels (2.48 ± 0.51), the IT scores in the medication-off/stimulator-on condition were most improved by 11.3% at 6 months follow-up (from 2.48 ± 0.51 to 2.20 ± 0.42, $t = 2.628$, $p = 0.020$); the scores at 12 months were lightly improved (improved

Fig. 1. a Odor IT of PD patients with olfactory dysfunction was significantly improved at 6 and 12 months after surgery in the medication-off/stimulator-on condition compared to the stimulation-off condition. Odor DT remained unchanged. **b** When compared with presurgical scores, postsurgical IT scores in the medication-off/stimulator-on condition at 6 months were significantly reduced ($t = 2.628$, $p = 0.020$). A similar trend was observed at the 12-month follow-up, although differences did not reach statistical significance ($t = 1.641$, $p = 0.123$). Odor DT remained unchanged.

Table 3. Comparison of odor function scores presurgery and 6 and 12 months postsurgery (mean ± SD)

	Presurgery medication- off	Postsurgery medication-off/stimulator-on			
		6 months	p value	12 months	p value
DT	1.63 ± 0.39	1.65 ± 0.35	$t = 0.807$ $p = 0.433$	1.71 ± 0.36	$t = 1.323$ $p = 0.207$
IT	2.48 ± 0.51	2.20 ± 0.42	$t = 2.628$ $p = 0.020$	2.28 ± 0.31	$t = 1.641$ $p = 0.123$

p value: postsurgery 6 and 12 months versus presurgery, respectively.

by 8%) but were not significantly different (from 2.48 ± 0.51 to 2.28 ± 0.31 , $t = 1.641$, $p = 0.123$) (table 3; fig. 1b).

Correlational analyses demonstrated that measurements of olfactory functions were not correlated with the UPDRS motor scores, ADL scores, disease duration or patients' age ($0.908 > p > 0.190$).

Discussion

In the present study we found that STN DBS could effectively improve odor IT in PD patients, but could not improve DT. These results are consistent with those of Hummel et al. [27] who reported findings from 9 cases of olfactory dysfunction in PD patients using three tests of olfactory function, including odor threshold, odor dis-

crimination, and odor identification. In patients with STN DBS, in the medication-off/stimulator-on condition, these authors found that odor discrimination was obviously improved whereas odor threshold was not. Taken with our findings, although the olfactory tests were not the same and amount of samples was small, the results indicate that STN DBS can effectively improve odor IT in PD.

Olfactory transmission originates from the olfactory cells, and is then transmitted to the olfactory nerves, OB, olfactory tract, AON and then to the primary olfactory centers (piriform cortex, entorhinal cortex, peripheral cortex of amygdaloid body) [28, 29]. These regions are thought to be an important integration site for the sense of smell, emotions, and memory [19, 20]. Information is then propagated to the secondary olfactory center (the orbitofrontal cortex, insular and hippocampus) [28, 30, 31]. The earliest LBs appear in the OB and the AON, causing alterations to the local neuronal architecture and neuronal degeneration. Subsequently, lesions the olfactory network, olfactory dysfunction, and OB pathology become more severe with increasing Braak stages [8, 9], although olfactory deficits do not correlate with the depth of olfactory sulcus in this time [7]. An autopsy study also confirmed that neuronal loss in the OB and AON and olfactory dysfunction in PD patients is associated with the presence of LBs [26]. A recent study found that the olfactory system represents a key induction site for neuropathological processes in PD [10]. Together these studies provide strong evidence that the pathological changes to the OB and AON underlie impaired olfaction in the early stages of PD. However, in advanced PD (e.g. Braak stages 5 and 6), the LB pathology progresses into the

higher-order association fields of the mesocortex and neocortex, such as the hippocampus, pyriform and orbitofrontal cortices [8, 9], thereby influencing information processing and integration in olfaction.

The STN is not directly involved with olfactory perception, although fibers involved in the production, integration, and transmission of olfactory information are located in numerous cortical and subcortical regions sharing vast connections with the STN [27]. Although some authors argue that STN DBS increases drives STN output to the GPi [32], STN DBS may decrease GPi inhibition of thalamic excitability through the basal ganglia-thalamic-cortical (BG-Th-Ctx) projections. This may therefore increase neuronal activity in the orbitofrontal and primary olfactory cortex, regions that are relevant to the integration of olfactory information. These changes may underlie the observed changes in olfactory IT.

Because motor symptoms improve following STN DBS, it is often the case that higher-level cognitive functions, including attention, activity, mood, and cognitive flexibility are similarly improved, while tension, fatigue, depression, and anxiety are reduced [33–38]. These improvements of somatic and psychiatric symptoms may increase the olfactory sensitivity of PD patients. The prefrontal lobe and cingulate gyrus are closely related to mood and are easily influenced by odor [20]. PET studies suggested that blood flow to the prefrontal cortex and anterior cingulate gyrus are increased following STN DBS [39]. However, it remains unclear why the odor IT improved but the odor DT did not. It is possible that odor DT is a low-level marker of olfactory function and is related to the degree of pathological impairment of the OB and AON [40–42]. Because these structures were damaged in early stages of PD [8, 9], stimulation may not be able to impact the function of these areas. By contrast, olfactory identification arises through perception, discrimination, recognition, and denomination of odors, which is not only related to an intact higher-order olfactory center (the hippocampus, orbitofrontal, insular and inferior lateral frontal cortex [40]) but also to higher-level cognitive functioning [12, 40, 41]. These cortical regions are relevant to olfactory identification [41] and are only damaged in advanced PD (e.g. Braak stages 5 and 6). A previous study demonstrated that, when PD patients lose all olfactory functioning, and olfactory pathways and olfactory center are completely damaged, olfactory DT increases maximally and DBS did not improve olfactory dysfunction [27].

Although the role of DA in the olfactory deficits in PD is contentious [4, 11, 23–26], using SPECT, Siderowf et al.

[43] demonstrated a close correlation between dopamine transporter density in the striatum and odor identification deficits in the early stages of PD. A recent study suggested that a combination of olfactory testing and transcranial sonography of the substantia nigra and ^{123}I -FP-CIT SPECT imaging may constitute a screening tool for the risk to develop idiopathic PD [44]. Two additional clinical studies also supported this viewpoint [5, 45]. These results revealed that dysosmia in PD patients is related to nigrostriatal function, and that olfactory IT is related to striatal DA metabolism. Although STN DBS does not change DA levels in brain, it may increase striatal DA release and metabolism in the striatum [46, 47]. This indicates that STN DBS may increase striatal DA metabolism and improve functional disturbances in the DA circuit by regulating abnormal excitability of STN [46, 47]. Additionally, PET studies suggest that bilateral STN DBS increases glucose metabolism bilaterally in the lentiform nucleus, midbrain, pons cerebellum, anterior cingulate gyrus, supplementary motor area of the prefrontal lobe, premotor area, and parietal-occipital cortex [39, 48, 49]. Increasing glucose metabolism in these areas indicates an increase in neuronal activity, perhaps underlying the improved olfaction due to increases in these higher-order somatosensory association cortical regions. Therefore, it is reasonable to explain the reason why the DBS-on condition can improve olfactory function and that the DBS-off condition cannot. When compared with presurgical levels, the odor IT scores in the medication-off/stimulator-on condition were most improved (by 11.3%) at 6 months follow-up; the scores at 12 months were slightly improved (improved by 8%) but were not significantly different ($p > 0.05$). These findings demonstrated that DBS could not recover dysosmia in PD patients and could only slightly improve olfactory identification function when stimulated.

In summary, STN DBS can significantly improve olfactory cognitive function in patients with PD. The possible mechanisms include an improvement in striatal metabolism and neuronal activity in the orbitofrontal cortex mediated by STN DBS, as well as increased glucose metabolism in the striatum, midbrain, cingulate gyrus, and motor and higher-order somatosensory association cortices.

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