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Olfactory function in Parkinson's Disease – effects of training

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Background – Up to 90% of patients with Parkinson's disease (PD) exhibit olfactory dysfunction, but little is known about the effects of olfactory training. The study aim was to investigate whether the ability to identify olfactory stimuli can be improved by means of a brief training session. Furthermore, the impact of hyposmia on quality of life in PD was investigated by means of a questionnaire. *Methods* – Olfactory function was rated in 34 patients with PD and in 26 controls before and after a training session. An additional 20 patients with PD served as a control group and were tested twice without an intervening training session. Long-term effects were evaluated in a small subset of patients. Cognitive tests and DaT SPECT scans were performed. *Results* – We demonstrated significant same-day and long-term training effects in trained PD patients compared with non-trained PD patients. A slightly significant correlation was seen between the training effect and DaT putamen values, but not with cognitive test scores. Furthermore, patients with PD reported that hyposmia significantly decreased their quality of life. *Conclusions* – Patients with PD improved the number of correctly identified odors in an olfactory test through a brief training session. Olfactory training may have potential in rehabilitation of patients with PD.

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Key words: hyposmia; olfaction; Parkinson's disease; single photon emission computed tomography (SPECT); training effect

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Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative condition, characterized by motor symptoms of bradykinesia, tremor, and rigidity, but also a number of non-motor signs including hyposmia (1–3). Up to 90% of patients with PD exhibit marked olfactory dysfunction (4–7), which is often present prior to onset of motor symptoms (2, 5, 6, 8–11), and olfaction tests have been suggested as a preclinical screening tool for identifying early, pro-dromal PD (12). Thus, olfactory testing has been suggested as a supporting diagnostic tool (11, 13, 14). Several studies have highlighted the importance of training and rehabilitation in PD, including speech and memory training as well as physical therapy strategies (15–17). However, the feasibility of olfactory training has received little attention.

Several studies have investigated the impact of impaired olfaction on quality of life (QoL) in other patient groups. These studies generally reported a higher level of disability and lower QoL than the background population of healthy elderly (1, 18, 19). Hyposmic/anosmic patients were also more likely to experience mild-to-severe depression (20). Patients who improved olfactory sense after treatment displayed improved QoL. In the context of PD, Politis et al. reported that the loss of smell and taste was the fifth most troublesome symptom overall among 92 early patients with PD, and it was rated as the second most bothersome non-motor symptom (21). However, little is known about the specific impact of hyposmia on QoL in PD, or whether patients with PD can improve olfactory function through training.

This study was conducted to investigate whether patients with PD can improve their ability to identify olfactory stimuli by means of a brief olfactory training session. Long-term effect was evaluated for a subset of patients after a 1-month follow-up period. Neuropsychological

tests were performed to investigate associations between improvements in olfactory sense and memory-related functions. Furthermore, patients were asked to rate their olfactory problem and to evaluate whether a potentially improved olfactory function would impact their QoL.

Materials & methods

Ethics statement

Participants provided written informed consent. The study was approved by the Danish National Committee on Research Ethics.

Subjects

We recruited 54 PD patients with decreased olfactory sense and 26 healthy controls without olfactory or neurological disorders. All patients with PD were diagnosed by movement disorder specialists according to established diagnostic criteria (22). Thirty-four patients with PD were enrolled as the olfactory training group (PD-training), 20 patients with PD served as a PD control group (PD-control), and were not exposed to olfactory training. At the time of olfactory testing, the patients received the following anti-parkinsonian medication: *PD-training*: none (n = 2), levodopa (n = 15), MAOB inhibitor (n = 1), dopamine agonist (n = 3), levodopa + MAOB inhibitor (n = 1), MAOB inhibitor + dopamine agonist (n = 4), levodopa + MAOB inhibitor + dopamine agonist (n = 3), levodopa + COMT-inhibitor + dopamine agonist (n = 2), levodopa + COMT-inhibitor + MAOB inhibitor + dopamine agonist (n = 1), levodopa + dopamine agonist (n = 2). *PD-control*: none (n = 11), levodopa (n = 5), MAOB inhibitor (n = 1), levodopa + COMT-inhibitor (n = 1), levodopa + MAOB inhibitor + COMT-inhibitor (n = 1), levodopa + dopamine agonist (n = 1). Approximately 9 months after olfactory testing, 18 of 20 patients in the PD-control group received anti-parkinsonian treatment. All subjects displayed a symptomatic response to their medication.

Questionnaire

Patients were asked to answer a mini-questionnaire regarding hyposmia and QoL. On a scale from 1 to 10, patients rated the consequence of their hyposmia on QoL in general – and whether they believed that an improved sense of smell/taste through training would positively impact their QoL. They were also enquired about their interest in participating in future olfactory and gustatory training regimes, if a beneficial long-term effect of this training had been demonstrated.

DaT SPECT

^{123}I-FP-CIT Dopamine Transporter (DaT) imaging was performed on 53 of 54 patients with PD, as described previously (23). In short, 3 h after intravenous administration of 150 MBq ^{123}I-FP-CIT, a 40-min recording was performed on a dual-head single photon emission computed tomography (SPECT)/CT gamma camera (Siemens Symbia T16, Erlangen, Germany).

Qualitative and quantitative analyses were performed using Hermes BRASS™ software (Hermes Medical Solutions, Stockholm, Sweden). Using occipital cortex as reference, specific binding ratios for caudate and putamen were calculated and compared to an in-house normal reference database.

Olfactory testing

Using the 'Sniffin' Sticks', 16-item smell test (Burghart, Wedel, Germany), all subjects were tested in a well-ventilated, quiet environment. Sticks were held 2 cm from the nostrils and presented with an interval of 20–30 s. The number of correct responses was scored from 0 to 16. All tests were performed by the same researcher (KK).

Odor discrimination – This test was performed to screen the subjects' ability to register the 16 Sniffin' Sticks odors at all. Subjects were blindfolded and presented to 3 × 16 odors, three at a time. Each triplet consisted of one odor-filled stick and two empty sticks. Subjects were instructed to select the stick containing the odor, but without naming or recognizing it.

Odor identification and training – Odor identification test was performed to examine each subject's ability to identify different odors. The 34 PD-training patients and the healthy control group were tested before (OI-1) and after (OI-2) a training session. The 20 PD-control patients were also tested twice (OI-1 and OI-2) before and after a 2-h break, but without an intervening training session. Subjects were presented to the 16 odors and instructed to choose the correct name of the odor among four possible options (forced choice test). Odors were presented in random order

before and after training. The training consisted of two sessions of each 10 min. – with a 10-min. break. During training, the 16 odors were presented one by one in random order. Accompanying each odor was a verbal and visual matching description, for example, when presented with the 'lemon' odor, the subjects were given an image of a lemon with 'lemon' written on it. To examine a potential long-term training effect, a third test (OI-3) was performed on eight patients from the PD-training group, who had displayed an initial improvement of three or more correct odors on the OI-2. The retest was performed after approximately 1 month.

Cognitive functions

All subjects were tested using the Mini-Mental Status Examination (MMSE)(24). The PD-training group and healthy controls were also tested using the Rey Auditory Verbal Learning Test (RAVLT)(25, 26) and the Boston Naming Test (BNT) (27). The first is a test of verbal learning and memory and consists of five presentations of a 15-item wordlist. Recall is administered after each presentation and a delayed recall after 30 min. Finally, a recognition trial was applied, where the participant had to indicate, which of 50 words were on the wordlist to be memorized. Assessment of confrontational naming ability was tested using the BNT, wherein participants were asked to name 30 line drawings.

Statistics

Demographic and clinical data were tested using unpaired *t*-tests and Fisher's exact test as appropriate. Training effects were assessed by paired *t*-tests, and linear regression was used to compare training effect across groups while adjusting for other markers. Associations between improvement in the PD-training subjects' olfactory score (OI-2 – OI-1) and their interest in olfactory training as well as their expectation concerning impact on QoL were investigated by one-way ANOVA tests.

Results

Table 1 shows demographic and clinical data of all subjects. All DaT SPECT scans were pathological, which reinforces the clinical diagnosis of PD. Most patients with PD had a near-normal performance on odor discrimination, demonstrating that they were able to detect most odors, even if not able to correctly name them. As expected, the patients with PD displayed markedly decreased odor identification on the initial test (OI-1). Table 2 summarizes the results of the mini-questionnaire. In average, the patients with PD were moderately bothered by hyposmia, and 52% expressed that improved olfactory and gustatory sense would have a positive effect on their QoL. There was no association between the PD subjects' subjective interest in improving their olfactory sense (i.e., question 2 in Table 2) and their actual improvement (ANOVA; $P = 0.52$), or between the expected impact on QoL (question 3 in Table 2) and their improvement (ANOVA; $P = 0.88$).

Figure 1A illustrates the immediate same-day effect of training in the PD-training group. A clear significant effect of training was detected ($P = 0.0002$). This finding was robust in using both paired t-test and logistic regression with correctness as outcome and session/subject as

Table 1 Demographic and clinical data of patients with Parkinson's disease (PD) and healthy controls (HC)

	PDt ($n = 34$)	PDc ($n = 20$)	HC ($n = 26$)	P (PDt/PDc)	P (PDt/HC)
Sex, m/f (% of male)	20/14 (58.8)	12/8 (60.0)	14/12 (53.8)	0.93	0.79
Age, year	64.2 ± 8.2	67.0 ± 7.3	62.7 ± 8.9	0.1	0.5
Age disease onset, year	60.2 ± 8.5	65.3 ± 7.7		**0.03**	
Disease duration, year	4.0 ± 3.5	2.7 ± 2.9		0.15	
Symptoms (uni-/bilateral)	27/7	15/5		0.71	
MMSE	28.3 ± 2.2	28.7 ± 1.5	28.8 ± 1.3	0.50	0.32
BNT	27.1 ± 2.9		28.5 ± 1.3		**0.02**
RAVLT, z-score$_{total}$	−0.52 ± 0.86		−0.01 ± 0.86		**0.03**
Odor discrimination	14.1 ± 2.9	14.1 ± 3.0	16.0 ± 0.0	0.94	**0.002**
Odor identification (OI-1)	6.8 ± 2.7	7.8 ± 2.7	13.4 ± 1.7	0.23	**<0.0001**
Odor identification (OI-2)	9.0 ± 3.4	7.9 ± 2.5	14.6 ± 1.3	0.21	**<0.0001**
Odor identification (OI-3)	9.0 ± 3.4				

Data given as mean ± SD. PDt = patients with PD exposed to training. PDc = patients with PD not exposed to training. The fourth and fifth columns denote *P*-values from statistical group comparisons of PDt vs PDc and PDt vs HC.
Bold marked values indicates a statistically significant difference.

Table 2 Results of mini-questionnaire

Question	Answer
1. How does hyposmia affect your daily life? (rate 1–10)	3.8 ± 2.8*
2. Would you be interested in improving your sense of smell and taste by training?	Yes: 56% No: 8% Don't know: 36%
3. Do you think this would improve your quality of life?	Yes: 52% No: 6% Don't know: 42%

Influence of hyposmia on quality of life (QoL) was rated on a 1–10 scale, 1 being 'not at all', and '10' being 'to an extreme degree'.
*Data given as mean ± SD.

Table 3 Data of olfactory test scores in patients with Parkinson's disease (PD) and healthy controls (HC)

	Mean of difference	CI (95%)	*P*
Same day tests			
PDt (OI-1 to OI-2) with training	2.176	3.251; 1.102	**0.0002**
HC (OI-1 to OI-2) with training	1.154	1.744; 0.564	**0.0005**
PDc (OI-1 to OI-2) without training	−0.1500	0.4032; −0.7032	0.577
Long-term effect			
PDt (OI-1 to OI-3)	2.375	3.711; 1.039	**0.004**

PDt = patients with PD exposed to training. PDc = patients with PD not exposed to training.

fixed/random effects, respectively. To obtain an initial assessment of potential long-term effects of training, we retested a small subset of the PD-training patients. They were tested 29–51 days after initial testing, and a significant long-term training effect was detected when comparing OI-1 and OI-3 (Fig. 1B; $P = 0.004$).

The group of healthy controls also exhibited a significant same-day training effect (Table 3). The training effect was only half the magnitude when compared to the PD group, although the group difference in improvement was not statistically significant ($P = 0.124$). The difference in magnitudes most likely represents a 'ceiling effect' due to the high baseline olfactory performance of the healthy subjects. The PD-control group showed no significant difference in test scores between OI-1 and OI-2 (Table 3).

Concerning the neuropsychological tests, the PD-training patients displayed decreased scores on BNT and RAVLT (Table 1). Using multiple linear regression, we tested dependence of these neuropsychological test scores and of the DaT scores on the training effect in the PD-training group. In the initial analyses, the DaT SPECT putamen values displayed a significant positive relationship to the training effect ($P = 0.040$), while the BNT scores exhibited a near-significant negative effect on the training effect ($P = 0.063$). The RAVLT z-score was clearly non-significant ($P = 0.53$). However, we noted that none of the three indices were significant in univariate models, and a *F*-test for reduction to a model with only an intercept was non-significant ($P = 0.11$). Thus, we could not demonstrate a substantial net effect of the auxiliary markers on the training effect.

Discussion

We demonstrated that patients with PD can improve the number of correctly identified odors subsequent to a brief training session. Preliminary results also suggest that this effect may persist for 1 month (Fig. 1B). In addition, the PD-control group displayed no significant difference between OI-1 and OI-2. This result supports that the observed training effect in the PD-training group is reliable and not a spurious effect due to simply being exposed to the olfactory test several times. This interpretation is further supported by a previous study, in which 35 patients with PD were tested twice during 12 weeks with no intervening training and no improvement was observed (28).

Another study reported that hyposmic patients with PD could improve olfactory function by specifically training their sniffing technique (29). It would be interesting to add such "sniffing

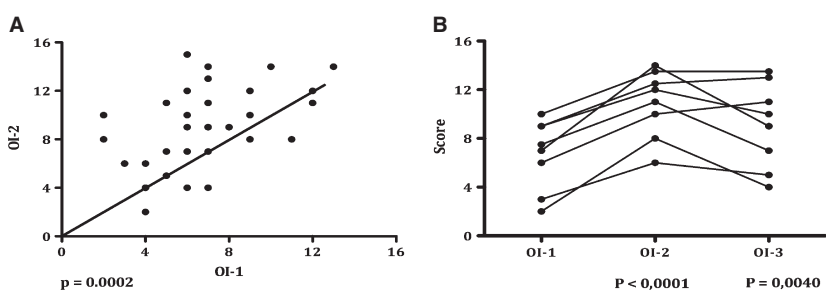

Figure 1. Odor identification in the PD-training group. (A) Immediate training effect demonstrated by test scores for OI-1 and OI-2. (B) Long-term effect in eight PD-training patients demonstrated by test scores for OI-1, OI-2, and OI-3.

training" to our training regime to investigate whether this could improve olfaction further. Recently, Haehner et al. reported that patients with PD, who exposed themselves to four odors daily for 12 weeks, displayed significant improvement on the Sniffin' Sticks *discrimination* subscore, and near-significant improvement on *identification* (28). The purpose of that study was to demonstrate that specific training on only four odors can influence the general performance on several olfactory parameters. By comparison, we employed training on the full 16-item battery – specifically targeting the *identification* subscore. Thus, our study can be construed as an investigation of olfactory memory, and the results suggest that olfactory memory of specific odors can indeed be strengthened by means of a targeted training regime.

The present pilot study was designed as an initial 'proof-of-concept study' to measure olfactory improvement subsequent to a brief training session. Thus, we did not attempt to measure any consequences on the patients' QoL, as we found it improbable that such brief training would have measurable effects. However, the results of the mini-questionnaire support the assumption that hyposmia negatively affects patients with PD in general, as previously reported by Politis et al. (21). More than 50% of our study subjects expressed an interest in olfactory training and opined that improved olfactory and gustatory function could potentially improve their QoL. Based on these observations, we speculate that hyposmia may affect patient QoL to a larger extent than previously appreciated. Thus, future large-scale studies are warranted to address whether training-induced improvement in olfactory/gustatory sense positively affects the QoL in patients with PD.

We initially hypothesized that there could be correlations between training-induced improvements in olfactory sense and learning abilities in other cognitive domains, specifically verbal learning. However, we did not see any correlation between improved olfaction and test scores of the RAVLT. Significant and near-significant correlations were initially detected between the DaT SPECT scores, BNT scores, and olfactory improvement, but these effects were deemed to be minor at best, and probably insignificant. Of note, DaT SPECT was mainly used as an additional verification of the PD diagnosis in the patient groups. Our examination of potential correlation between DaT SPECT and other parameters was secondary to the study of olfactory training effect *per se*.

Our study has some limitations. We only investigated training effects on olfactory identification, but not on discrimination scores. Thus, we cannot comment on potential training effects on this olfactory parameter. Also, our sample size was modest – particularly in the 1-month follow-up patient group. This impairs the generalizability of those results. In addition, none of the participants in the PD-control or healthy control groups performed the OI-3 follow-up test at 1 month. Therefore, we cannot exclude that the long-term effect seen in the PD-training group may be incidental.

Formal UPDRS evaluation was not performed in this study, so the severity of motor symptoms was less accurately determined. However, all patients with PD were diagnosed by movement disorder specialists, and all had a pathological DaT SPECT. The main goal of this pilot study was to investigate whether patients with PD in general were able to improve olfactory identification by means of a simple training regime. Thus, we do not consider the lack of UPDRS scores a major limitation.

In summary, we demonstrated that patients with PD can improve the number of correctly identified odors in a validated olfactory test through a brief training session and that this training effect may persist after 1 month, although the latter result was based on only eight PD subjects and needs replication including a control group.

Future studies are needed to clarify whether intensified training regimes could improve the olfactory and perhaps gustatory senses even further, and, importantly, attempt to measure the impact on the patients' QoL. Thus, olfactory and gustatory training could potentially be included in future rehabilitation programs of patients with PD.

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None related to this study.

Author roles

Karoline Knudsen: Research project; organization, data collection; Statistical analysis; execution; Manuscript; writing of

first draft, review and critique, approval of final edition. Malene Flensborg Damholdt: Research project; conception, organization; Statistical analysis; design; Manuscript; review and critique, approval of final edition. Kim Mouridsen: Research project; conception; Statistical analysis; design, execution, review and critique; Manuscript; review and critique, approval of final edition. Per Borghammer: Research project; conception, organization, fund raising; Statistical analysis; design, execution, review and critique; Manuscript; writing of first draft, review and critique, approval of final edition

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