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Effectiveness of olfactory training in COVID-19 patients with olfactory dysfunction: a prospective study

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Abstract

Objectives To investigate effectiveness of olfactory training (OT) in COVID-19 patients with persistent olfactory dysfunction (OD).

Methods From March 2020 to March 2022, COVID-19 patients with OD were prospectively followed in three European medical centers for a period of 18 months. A standardized OT protocol were recommended to patients. Patient-reported outcome questionnaires and psychophysical evaluations were used to evaluate olfaction at baseline, 6, 12, and 18 months after the start of OT. The evolution of olfactory outcome was compared according to the adherence to the OT protocol.

Results Fifty-seven patients completed the evaluations. Thirty-two patients fully adhered to the OT, while 25 did not adhere. The psychophysical scores significantly improved from baseline to 6-month post-infection in both groups. In the OT group, the psychophysical scores continued to significantly improve from 6 to 12 months after the start of OT ($p = 0.032$). The mean duration of OT was 15.4 weeks. The mean delay of patient recovery perception was comparable between groups (27.4 weeks). The occurrence of cacosmia (35.1%) and parosmia (43.9%) throughout the follow-up period was comparable between groups. There proportion of phantosmia was higher in training (34.4%) compared with no-OT (16.0%; $p = 0.007$) group. The baseline Sniffin'Sticks tests was positively associated with the 6-month Sniffin'Sticks tests ($r_s = 0.685$; $p < 0.001$) and negatively associated with the time of recovery ($r_s = -0.369$; $p = 0.034$).

Conclusions The adherence to an OT protocol was associated with better mid-term improvement of psychophysical scores. Future large-cohort randomized-controlled studies are needed to confirm the effectiveness of OT in COVID-19 patients.

Keywords COVID-19 · Otolaryngology · Rhinology · Coronavirus · SARS-CoV-2 · Training · Olfactory · Smell · Recovery

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Introduction

Olfactory dysfunction (OD) is one of the most common COVID-19 symptoms, accounting for 30–86% of cases [1–3]. Most cases fully recovery olfactory function within a month but in 15–46% of cases patients develop persistent OD [4–6]. To date, There are no guidelines for the treatment of COVID-19-related OD but many studies suggested that olfactory training (OT) may improve olfactory function in patients with post-viral or post-traumatic loss of smell [1, 6–8].

The aim of this study was to investigate the effectiveness of OT in COVID-19 patients with persistent OD.

Methods

Setting and patients

From March 2020 to June 2020, 97 patients with RT-PCR-confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and OD were prospectively recruited from three hospital (Dour Medical Center, CHU Saint-Pierre of Brussels and EpiCURA hospital of Baudour (Belgium)). Patients included in this study were part of a study cohort in which we wanted to prospectively monitor OD recovery (unpublished data). In this cohort, an olfactory training was proposed to all patients according to a standardized protocol [8, 9]. From this large cohort of patients, we retrospectively extracted the data of patients who met the following criteria:

- Patients with persistent OD at 3-month post-COVID-19. The OD was confirmed with identification Sniffin'Sticks test (Medisense, Groningen, Netherlands), which reported a score < 12.
- Patients who completed all evaluation timepoints throughout the follow-up, which consisted of psychophysical evaluations at baseline, 6, 12, and 18 months after the start of the OT.
- Patients who carefully reported the adherence to the olfactory training protocol, e.g., number of daily training session, type of odor used, etc. Patients were, therefore, encouraged to use a notepad to precisely report the adherence to the olfactory protocol.

From the selected patients according to these criteria, two groups of patients were composed. The first group included patients who adhered to the olfactory training protocol (at least twice daily sessions for 3 months; Fig. 1) [9]. The second group included patients who did not adhere to the olfactory training protocol (OT performed less than 1 week). Patients who recognized to adhere to the training occasionally or a few weeks in the first weeks of the study were excluded. Patients were excluded if they presented a history of previous olfactory dysfunction, chronic and allergic rhinosinusitis, nasal or olfactory cleft surgery, radiotherapy, trauma to the nasal cavities or a second SARS-CoV-2 infection throughout the follow-up.

The local ethics committee approved the study protocol (EC-2020-2303). The electronic informed consent was obtained.

Epidemiological and clinical outcomes

The following epidemiological and clinical data were collected through a standardized online questionnaire: age; gender; ethnicity; comorbidities and tobacco consumption. The prevalence and severity of COVID-19 symptoms were investigated with the COVID-19 symptom index, which is a 26-item patient-reported outcome questionnaire assessing common COVID-19 symptoms [10]. The symptom severity of general and otolaryngological symptoms was assessed as 0 (no symptom), 1 (mild symptom), 2 (moderate symptom) 3 (severe symptom) and 4 (very severe symptom), while loss of smell and taste were rated as total (2), partial (1) or absent (0). The total COVID-19 symptom index score ranges from 0 to 100. The French version of the sinonasal outcome tool-22 (SNOT-22) was used to evaluate nasal symptoms [11].

Olfactory function evaluations

The olfactory and gustatory questions were reported in the smell and taste component of the National Health and Nutrition Examination Survey [12]. The French version of the short version of Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) was used to assess the impact of OD on quality of life [13]. QODN is a 7-item patient-reported outcomes questionnaire assessing impact of smell changes on quality of life with a total scale ranging from 0 (no impact on quality of life) to 21 (important impact of quality of life) [13]. The psychophysical olfactory evaluations were performed within 2 weeks of the onset of the OD with the identification part of the Sniffin'Sticks tests. The score ranged from 0 (complete anosmia) to 16 (no olfactory disorder). According to recent studies, a score between 12 and 16 may be considered as normal. Hyposmia was defined as a score between 9 and 11, while and anosmia consisted of a score < 9 [14, 15]. The psychophysical evaluations were repeated at 6, 12, and 18 months after the start of the OT until scores returned to normal levels.

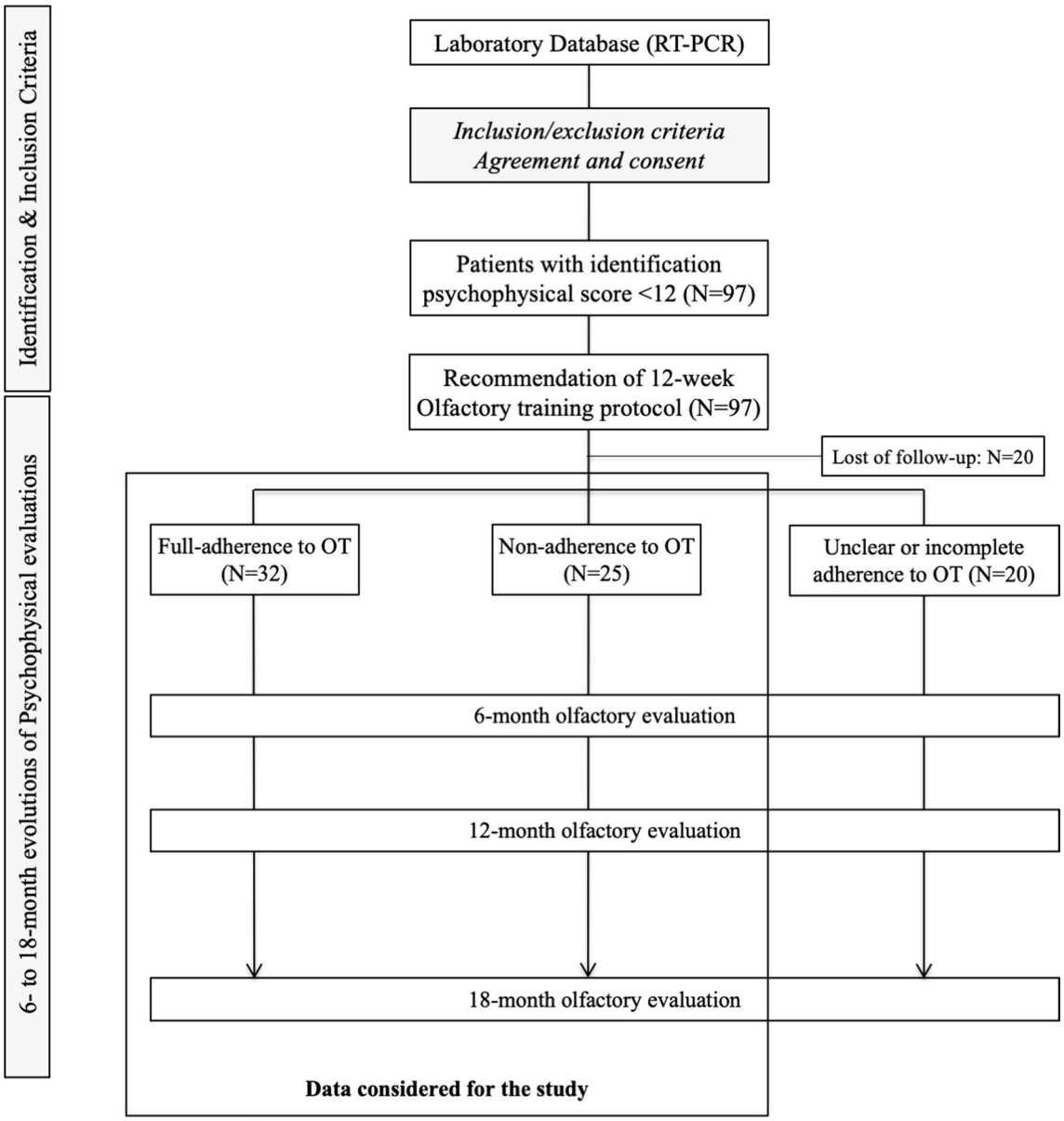

Fig. 1 Flow chart. *COVID-19* coronavirus disease 2019, *OT* olfactory training, *RT-PCR* reverse transcription polymerase chain reaction

Olfactory training

The olfactory training was started after the first psychophysical evaluation. The protocol was described in previous studies [8, 9]. In sum, patients exposed themselves to various odors at least twice daily. To the 4 traditional odors proposed by Hummel et al. [9] (rose, eucalyptus, lemon and cloves). They had to name the sniffed odor and reported the olfactory training protocol adherence to the physician in each consultation time with, at best, a notepad.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, v23.0; IBM Corp, Armonk, NY, USA). The evolution of olfactory function outcomes was studied with the Wilcoxon Rank test. The evolution of olfactory function was analyzed according to the adherence of patients to olfactory training (full adherence *versus* no-adherence). The relationship between epidemiological, clinical and olfactory function outcomes was analyzed with multivariate analysis.

Table 1 Epidemiological and clinical characteristics of patients

Clinical outcomes	All patients $N=57$	OT $N=32$	No OT $N=25$	p value
Age (mean, SD)	40.55 ± 11.66	41.39 ± 11.57	39.52 ± 11.71	NS
Gender (F/M)	23/34	22/10	12/13	NS
Comorbidities				
Diabetes	3 (5.3)	2 (6.3)	1 (4.0)	NS
Hypertension	4 (7.0)	2 (6.3)	2 (8.0)	NS
Hypothyroidy	5 (8.8)	3 (9.4)	2 (8.0)	NS
Allergic rhinitis	3 (5.3)	5 (15.6)	1 (4.0)	NS
Kidney insufficiency	0 (0)	0 (0)	1 (4.0)	NS
Reflux	5 (8.8)	3 (9.4)	2 (8.0)	NS
Asthma	5 (8.8)	2 (6.3)	3 (12.0)	NS
Heart insufficiency	1 (1.8)	0 (0)	1 (4.0)	NS
Depression	0 (0)	1 (3.1)	0 (0)	NS
Smoker (*N*, %)	6 (10.4)	2 (6.3)	4 (16.0)	NS
Allergic (*N*, %)	9 (15.8)	6 (18.8)	3 (12.0)	NS
COVID-19 symptom index				
Fever	0.20 ± 0.69	0.14 ± 0.70	0.27 ± 0.70	NS
Cough	0.51 ± 0.99	0.34 ± 0.99	0.73 ± 0.99	NS
Chest pain	0.33 ± 0.79	0.24 ± 0.80	0.45 ± 0.80	NS
Anorexia	0.43 ± 0.94	0.59 ± 0.95	0.24 ± 0.95	NS
Sputum/throat mucus	0.28 ± 0.73	0.32 ± 0.73	0.24 ± 0.73	NS
Arthralgia	0.54 ± 1.16	0.50 ± 1.17	0.60 ± 1.17	NS
Myalgia	0.52 ± 1.09	0.54 ± 1.10	0.50 ± 1.10	NS
Abdominal pain	0.22 ± 0.58	0.25 ± 0.59	0.18 ± 0.59	NS
Diarrhea	0.38 ± 0.85	0.43 ± 0.86	0.32 ± 0.86	NS
Nausea or vomiting	0.16 ± 0.65	0.07 ± 0.66	0.27 ± 0.66	NS
Headache	0.88 ± 1.20	0.82 ± 1.21	0.95 ± 1.21	NS
Fatigue	1.25 ± 1.31	1.34 ± 1.31	1.14 ± 1.32	NS
Urticaria	0.07 ± 0.33	0.14 ± 0.34	0.01 ± 0.34	NS
Conjunctivitis	0.25 ± 0.59	0.17 ± 0.60	0.36 ± 0.60	NS
Nasal obstruction	0.72 ± 0.98	0.76 ± 0.98	0.68 ± 0.98	NS
Rhinorrhea	0.57 ± 0.87	0.62 ± 0.88	0.50 ± 0.88	NS
Postnasal drip	0.41 ± 0.80	0.45 ± 0.81	0.36 ± 0.81	NS
Throat pain	0.20 ± 0.60	0.10 ± 0.60	0.32 ± 0.60	NS
Facial pressure/pain	0.30 ± 0.76	0.24 ± 0.76	0.36 ± 0.76	NS
Otalgia	0.33 ± 0.71	0.41 ± 0.71	0.23 ± 0.71	NS
Dysphagia	0.14 ± 0.49	0.03 ± 0.49	0.27 ± 0.49	NS
Dyspnea	0.29 ± 0.75	0.17 ± 0.76	0.45 ± 0.76	NS
Dysphonia	0.20 ± 0.58	0.28 ± 0.58	0.09 ± 0.58	NS
Smell loss	2.11 ± 1.82	2.36 ± 1.81	1.74 ± 1.82	NS
Taste loss	1.82 ± 1.51	2.28 ± 1.85	1.25 ± 1.84	NS

COVID-19 coronavirus disease 2019, *F/M* female/male, *N* number, *OT* olfactory training, *SD* standard deviation, *y* years old

Results

The data of 57 patients who completed the 18-month evaluations were retrieved (Fig. 1). Thirty-two patients adhered to the olfactory training, while 25 did not adhere. Forty patients were excluded, because they were lost of follow-up, or they partially adhere to the olfactory training protocol. The epidemiological and clinical features of patients are reported in Table 1. The mean age of patients was 40.6 ± 11.7 years. There were 23 males and 34 females. There were no significant differences between group regarding age, gender and comorbidities. The most

Table 2 Baseline smell and taste findings

Clinical outcomes	All patients $N=57$	OT $N=32$	No-OT $N=25$	p value
Onset of smell dysfunction				
Before the other symptoms	8 (14.0)	7 (21.9)	1 (4.0)	NS
Concurrent with other symptoms	14 (24.6)	7 (21.9)	7 (28.0)	NS
After the other symptoms	25 (43.9)	13 (40.6)	12 (48.0)	NS
Did not remember	10 (17.5)	5 (15.6)	5 (20.0)	NS
Taste dysfunction				
None	39 (68.4)	19 (59.4)	20 (80.0)	NS
Present	18 (31.6)	13 (40.6)	6 (24.0)	NS
Aroma dysfunction				
None	6 (10.5)	1 (3.1)	5 (20.0)	NS
Decrease	15 (26.3)	10 (31.3)	5 (20.0)	NS
Total loss	19 (33.3)	11 (34.4)	8 (32.0)	NS
Distorted	7 (12.3)	4 (12.5)	2 (8.0)	NS
Did not remember	1 (1.8)	5 (15.6)	5 (20.0)	NS
Smell sense dysfunction				
Total loss	31 (54.4)	17 (53.1)	14 (56.0)	NS
Partial loss	24 (42.1)	14 (43.8)	10 (40.0)	NS

COVID-19 coronavirus disease 2019, *M* mean, *N* number, *NS* non-significant, *OT* olfactory training

Table 3 Olfactory features throughout follow-up

Follow-up outcomes	All patients $N=57$	OT $N=32$	No-OT $N=25$	p value
Patient perception of recovery				
Total recovery of smell	26 (45.6)	12 (37.5)	14 (56.0)	NS
Partial recovery of smell	31 (54.4)	20 (62.5)	11 (44.0)	NS
Recovery time (*N* weeks, SD)	27.5 ± 26.4	30.2 ± 26.4	24.0 ± 26.7	NS
Training outcomes				
Daily session (*N*, SD)	14.1 ± 17.4	14.1 ± 17.4	–	–
Duration of training (*N* month, SD)	15.4 ± 10.3	15.4 ± 10.3	–	–
Follow-up disorders				
Cacosmia	20 (35.1)	11 (34.4)	9 (36.0)	NS
Duration (days)	106.9 ± 86.4	130.6 ± 88.0	76.4 ± 89.7	NS
Phantosmia	15 (26.3)	11 (34.4)	4 (16.0)	0.007
Duration (days)	233.6 ± 131.5	225.0 ± 131.5	225.0 ± 142.5	NS
Parosmia	25 (43.9)	17 (53.1)	8 (32.0)	NS
Duration (days)	135.2 ± 103.0	132.3 ± 106.8	142.3 ± 93.8	NS
Association disorder	16 (28.1)	11 (34.4)	5 (20.0)	NS
Medications (received)				
Alpha lipoic acid	8 (14.0)	5 (15.6)	3 (12.0)	NS
Vit A	4 (7.0)	4 (12.5)	0 (0)	NS
Vit B12	5 (8.8)	4 (12.5)	1 (4.0)	NS
Nasal corticosteroids	11 (19.3)	8 (25.0)	3 (12.0)	NS
Oral corticosteroids	6 (10.5)	4 (12.5)	2 (8.0)	NS

These features were evaluated throughout the follow-up and at the end of the study time (18-month post-onset of OD)

OT olfactory training, *QOD-NS* Questionnaire of Olfactory Disorders-Negative Statements, *SNOT-22* sino-nasal outcome 22

prevalent comorbidities were allergies (16%), reflux (9%) and asthma (9%). The mean COVID-19 symptom index was 8.8 ± 10.3 (range 0–54; Table 1). According to the sQOD-NS data, the OD negatively impacted patients in their daily life and social activity in 75.4%, leading to a social isolation in 78.9% of cases. Forty-five (78.9%) patients reported that they did not go to restaurant because of OD and related aroma dysfunction. The baseline patient-reported features of OD are described in Table 2. There were no significant epidemiological, clinical and baseline olfactory outcome differences between groups.

The features of olfactory training are available in Table 3. The mean duration of olfactory training was 15.4 weeks. The mean delay of patient recovery perception was 27.5 weeks. The occurrence of cacosmia and parosmia throughout the follow-up was comparable between groups. The proportion of phantosmia was significantly higher in patients who adhere to the training protocol compared with those who did not adhere ($p = 0.007$). Sixteen patients (28.1%) reported an association disorder, defined as the inability to name the odor that they sniff despite they smell something. A few patients received alpha-lipoic acid, vitamins, or corticosteroids during the first weeks of the OD (Table 3).

The evolution of psychophysical olfactory evaluations is reported in Table 4. The psychophysical scores significantly improved from baseline to 6-month post-infection in patients who did not adhere to olfactory training. After this timepoint evaluation, there was no longer improvement of identification psychophysical evaluations.

In the OT group, the psychophysical scores significantly improved from baseline to 12-month post-infection (Fig. 2).

The multivariate analysis reported that the baseline Sniffin'Sticks tests had a predictive value on the 6-month Sniffin'Sticks tests ($r_s = 0.685$; $p < 0.001$). The baseline Sniffin'Sticks tests reported significant negative association with the time of recovery ($r_s = -0.369$; $p = 0.034$). There were no significant associations between baseline clinical outcomes and the recovery of smell at each point times.

Discussion

The recovery of smell sense is a challenging issue in patients with OD related to COVID-19. In this study, patients who adhered to an OT protocol reported better 6–12-month evolution of Sniffin'Sticks tests than those who did not adhere to OT. Indeed, after 6 months, the olfaction evolution results of the non-OT group have been flat, which may support the usefulness of OT protocol in the olfactory recovery process. The findings of the present study are consistent with previous studies supporting the effectiveness of OT in patients with post-viral loss of olfactory sense [9, 16, 17]. In a systematic review, Yuan et al. reported that olfactory function of patients with post-viral loss of smell sense was significantly improved through the use of nasal corticosteroids or the adherence to an standardized or modified OT [17]. In 2018, Oleszkiewcz et al. observed that among patients with several causes of OD, the OT was more effective in post-infectious OD [16]. Our study is an additional investigation supporting the effectiveness of OT in post-viral loss of smell sense, with the particularity that the OD was related to SARS-CoV-2. Indeed, to the best of our knowledge, there is no similar study investigating the effectiveness of OT on hyposmic or anosmic COVID-19 individuals. Only Altundag et al. reported the effectiveness of a modified OT protocol on COVID-19 patients with parosmia but this profile of patients differed from ours (hyposmia–anosmia patients). From a pathophysiological standpoint, the repeated short-term exposure to odors may increase both the growth of olfactory receptor neurons and the expression of olfactory receptor in the olfactory cleft mucosa [9, 19]. The positive influence of OT may also involve olfactory bulb and brain changes [9, 20]. Thus, Gellrich et al. recently reported that the adherence to an OT was associated with an increase of gray matter volume of the hippocampus and the thalamus, which are both involved in the memory of olfactory stimuli [20].

In practice, we commonly meet OD patients with aroma disorders (retro-olfaction) and related eating disorders; most of them with parosmia [21]. This problem was highlighted in the present study with 75.4% and 78.9% of patients reporting a significant impact of OD on their daily life and social activity, respectively. Because the adherence to an OT was proposed to enhance the sensitivity of foods and beverages [9], the proposition of such protocol or a modified parosmia-protocol [18] makes particularly sense in these patients.

In this study, 35.1%, 26.3% and 43.9% of patients reported cacosmia, phantosmia or parosmia throughout the follow-up period, which corroborates the literature findings. The post-COVID-19 prevalence of phantosmia ranged from

Table 4 Evolution of psychophysical scores throughout follow-up

	Psychophysical scores throughout follow-up						
	Baseline	6 months	p value	12 months	p value	18 months	p value
No OT	6.9 ± 3.0	10.1 ± 3.7	0.003	11.3 ± 4.6	NS	12.9 ± 4.1	NS
OT	7.2 ± 2.7	10.2 ± 4.1	0.001	11.8 ± 3.3	0.032	14.1 ± 2.4	NS

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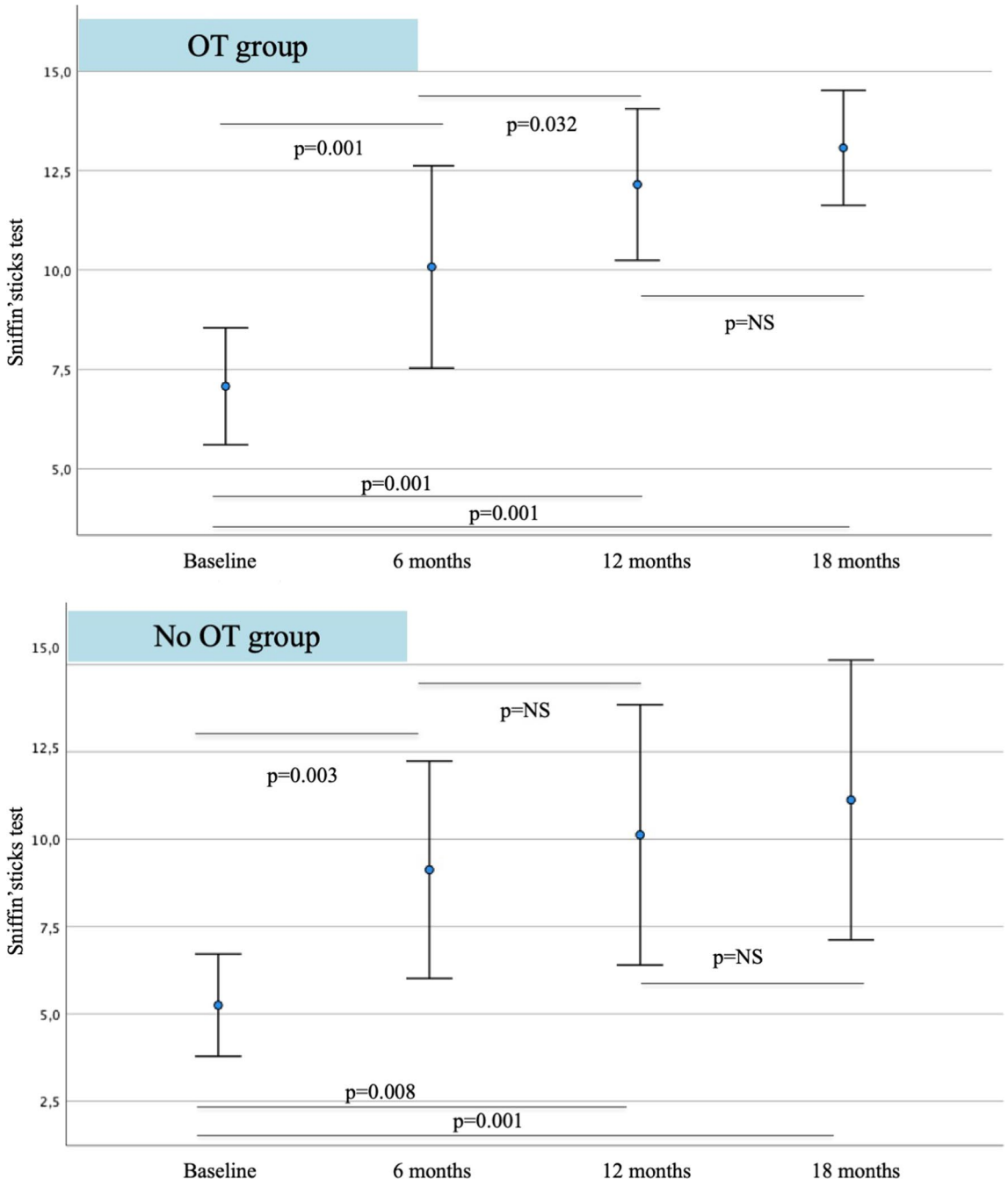

Fig. 2 Evolution of psychophysical scores throughout follow-up. The increase of psychophysical scores was significant from 6- to 12-month post-infection only in patients who adhered to olfactory training protocol (Wilcoxon Rank test)

20.5 to 48%, while 18–73% reported parosmia within the post-COVID-19 months [22–25]. Interestingly, we observed a higher proposition of phantosmia in the OT group compared to the control group. We did not find similar findings in the literature.

The low number of patients is the main limitation of the present study. The low number of patients was related to the exclusion of many patients who did not report details about the adherence of OT protocol or who missed an evaluation consultation. The lack of use of the threshold, discrimination and identification test (TDI, 48 pens) is another limitation, because TDI provides additional information about smell sense through the threshold and discrimination parts. Our team did not use TDI, because at the onset of the pandemic, it was difficult to perform any long testing evaluations regarding the patient consultation restrictions in the

medical centers of our country. These restrictions limited us in the realization of complete psychophysical evaluations, nasofibroscopy and imaging in COVID-19 patients included during the first European wave. The design of the study is another limitation. Precisely, the OT recommendation in all included patients (non-OT and OT groups) may be associated with a bias. Furthermore, since the No-OT group was recommended OT, one cannot assume that this group had so little exposure to the intervention.

The prospective design with several timepoints of olfactory evaluations (6, 12, and 18 months) is the main strength of the study. The evaluations of the patient adherence to the OT throughout the follow-up is an additional strength of the study. Indeed, to the best of our knowledge, there were no similar studies assessing the effectiveness of OT throughout the 18-month post-infection.

Conclusions

The adherence to an olfactory training protocol was associated with better mid-term improvement of psychophysical scores in patients with OD. Future large-cohort randomized-controlled studies are needed to confirm the effectiveness of OT in COVID-19 patients.

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Declarations

Conflict of interest The authors have no conflict of interest.

Research involving human participants and/or animals IRB was not required for this study.

Informed consent None.

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