Adherence to olfactory training improves orthonasal and retronasal olfaction in post-COVID-19 olfactory loss

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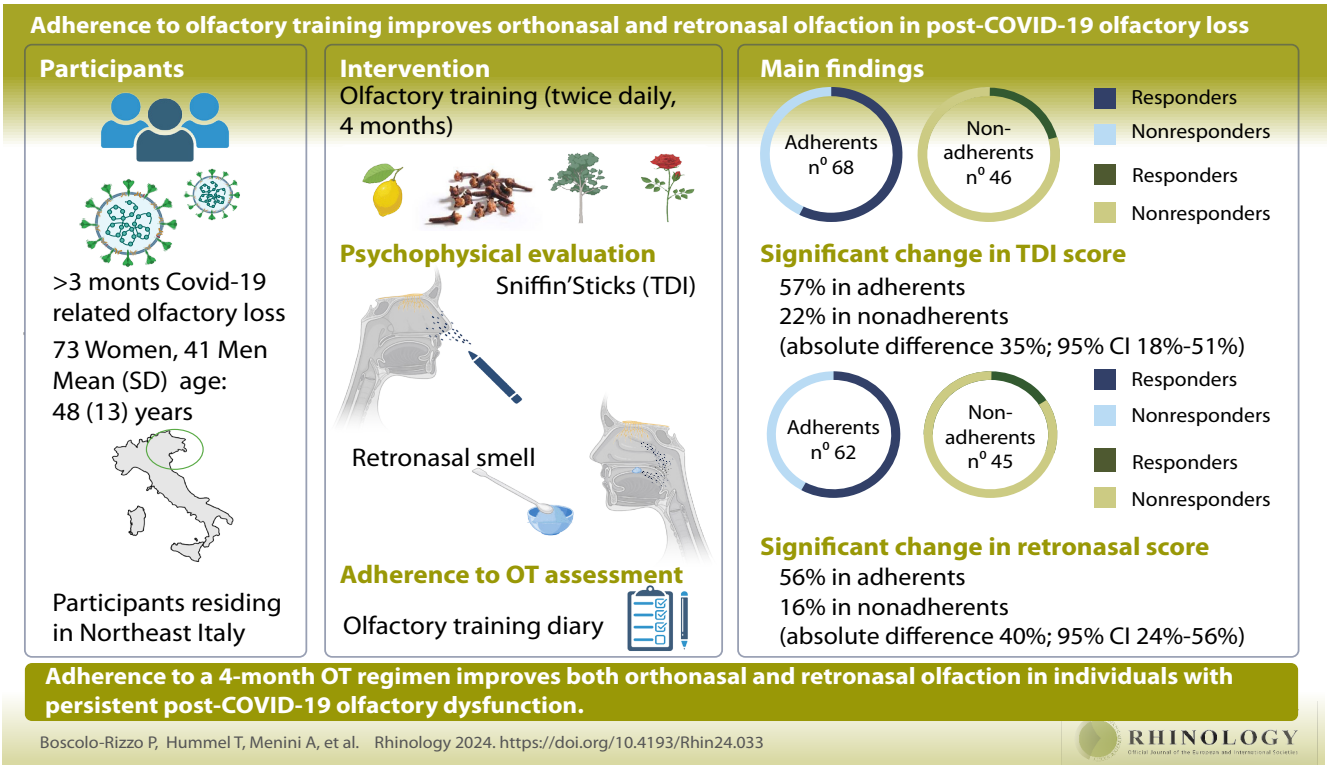

Abstract

Background: Olfactory loss (OL) has emerged as one of the most prevalent and debilitating symptoms of SARS-CoV-2 infection and long-COVID-19. The present prospective observational study aimed to evaluate the efficacy of olfactory training (OT) on orthonasal and retronasal olfactory function in a cohort of individuals with persistent post-COVID-19 OL.

Methodology: Participants with post-COVID-19 olfactory impairment underwent 4 months of OT, self-assessing their smell perception and undergoing comprehensive psychophysical evaluation of orthonasal and retronasal olfaction at baseline and after training. Orthonasal olfactory function was assessed using the extended Sniffin' Sticks test battery. Retronasal olfactory function was tested with powdered aromas.

Results: Among 114 participants with post-COVID-19 olfactory loss, adherence to OT was 60%. In adherents, the average increase in composite TDI score was 6.0 points compared to 2.6 points in non-adherents. Fifty-seven percent of adherent participants achieved a clinically significant improvement in TDI score (≥5.5 points), compared to 22% of non-adherents. In retronasal olfactory identification, 56% of adherents achieved a clinically significant improvement (≥4 points), compared to 16% of non-adherents.

Conclusion: Adherence to a 4-month OT regimen can yield clinically meaningful improvements in both orthonasal and retronasal olfactory function among individuals with persistent post-COVID-19 olfactory dysfunction.

Key words: anosmia, COVID-19, olfactory disorders, olfactory training, SARS-Cov-2, smell

Introduction

Olfactory loss (OL) has emerged as one of the most prevalent and debilitating symptoms of SARS-CoV-2 infection [1,2]. While most cases of COVID-19-associated OL resolve within a few weeks, a substantial proportion of individuals experience a self-reported and measured persistent olfactory dysfunction lasting several months or even years post-infection [3–5]. Long-term OL not only poses a severe burden on daily functioning but also carries profound psychological consequences, often culminating in depression, anxiety, and social isolation [6,7]. Despite the pressing need, therapeutic options for treating post-viral OL remain limited [8].

The olfactory system exhibits remarkable neuroplasticity with the peripheral olfactory pathways harbouring specialised regions that enable regeneration through the continuous integration of newly formed neurons derived from adult neural stem cells throughout life. At the same time, plasticity is also found in the central nervous olfactory system [9–13]. Olfactory training (OT), a simple and inexpensive therapy involving daily exposure to distinctive odours, has emerged as a promising approach to harness this neuroplastic potential [13–15]. Direct human studies examining the effects of OT on the molecular and cellular composition of the olfactory system are currently lacking; however, animal studies suggest that OT may upregulate the expression of olfactory receptors, anti-apoptotic genes, neurotrophic factors, stem cell, and synaptic plasticity genes, possibly aiding neurogenesis [13].

While the efficacy of OT has been demonstrated in various olfactory disorders [14,16–19], its application in the context of post-COVID-19 OL has been met with variable outcomes, potentially attributable to suboptimal adherence to the prescribed regimen, the timing of the training relative to the onset of symptoms and the severity of the OL [20–26].

This prospective observational study aims to evaluate the efficacy of OT on orthonasal and retronasal olfaction through a comprehensive olfactory function assessment in a cohort of individuals with persistent post-COVID-19 OL.

Materials and methods

Patient population

This prospective observational cohort study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethics committee for clinical experimentation of Friuli Venezia Giulia Region (CEUR-2020-Os-156). Informed consent was obtained verbally and in writing. Participants were recruited at the Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy. To be included, individuals had to be adults between 18 and 70 years old experiencing an ongoing olfactory impairment, defined as a threshold, discrimination, and identification (TDI) score <30.75, lasting for at least 3 months. The OL needed to be diagnosed within 2 weeks after contracting SARS-CoV-2 infection, as confirmed by positive results for SARS-CoV-2 RNA through polymerase chain reaction on nasopharyngeal and throat swabs. Individuals with previous head trauma, chronic rhinosinusitis, congenital anosmia, nasal polyps, or neurodegenerative disorders like Alzheimer's or Parkinson's disease were excluded from the study.

Olfactory training

Participants were invited to sniff, twice a day for 4 months, the 4 essential oils of rose, lemon, eucalyptus, and clove placed in amber-coloured jars for 10 seconds, with a 15-second rest between odours [14].

The patients had counseling with the otolaryngologist who stressed the importance of continuing with OT even in the absence of a subjective perception of improvement, and they were contacted by phone monthly to encourage them to continue with the training. Participants documented their OT sessions in a diary supplied by the researchers in which they recorded their training sessions every day. Adherence to the intervention protocol was defined as completing an average of 10 out of the prescribed 14 weekly sessions.

Self-assessment of chemosensory perception

Before psychophysical olfactory tests, each participant was asked to self-report their chemosensory perception, namely odour perception ("How would you rate your sense of smell?") using a 100 mm Visual Analogue Scales (VAS), ranging from 0 (no perception) to 100 (excellent perception).

Psychophysical evaluation

The evaluation was performed in silent and well-ventilated rooms at baseline and the end of the OT. To avoid chemosensory desensitization, all participants were instructed not to eat, drink, smoke, or brush their teeth up to 2 hours before participation in the measures.

Orthonasal olfactory function

Orthonasal olfactory function was measured using the validated extended Sniffin' Sticks test (SST) battery (Burghart Messtechnik, Holm, Germany) including phenylethyl-alcohol (PEA) odour thresholds (T), odour discrimination (D), and odour identification (I) (27). The maximum score for each of the 3 subsections of the SST is 16. Results are combined for a composite TDI score (range 1–48) and categorised as functional anosmia (TDI ≤ 16.0), hyposmia (16.25 - 30.5), or normosmia (TDI ≥ 30.75) [28]. The test has been validated and shown to have high test-retest reliability [29]. Testing was performed by the standardised testing protocol

Table 1. Demographic and clinical characteristics of the study population at baseline according with adherence to OT.

	Participants, No. (%)						
	All (n=114)		Adherent to OT protocol (n=68)		Not adherent to OT protocol (n=46)		p-value [a]
Age, mean (SD), y	48	(13)	49	(12)	46	(13)	0.272
Sex							
Female	73	(64)	44	(65)	29	(63)	0.856
Male	41	(36)	24	(35)	17	(37)	
Duration of OL, mean (SD), mo	9.5	(3.7)	9.4	(4.1)	9.6	(3.0)	0.732
Parosmia or phantosmia							
No	42	(37)	26	(35)	16	(38)	0.708
Yes	72	(63)	42	(62)	30	(65)	
VAS olfaction, mean (SD), mm	35	(25)	35	(25)	36	(26)	0.860
TDI score, mean (SD)	22.6	(6.0)	22.2	(6.3)	23.3	(5.4)	0.315
TDI score, category							
≤ 16.0	19	(17)	12	(18)	7	(15)	0.733
16.25 - 30.50	95	(83)	56	(82)	39	(85)	
Orthonasal identification score							
< 12	83	(73)	49	(72)	34	(74)	0.827
≥ 12	31	(27)	19	(28)	12	(26)	
Retronasal identification score							
< 12	61	(54)	37	(54)	24	(52)	0.814
≥ 12	53	(46)	31	(46)	22	(48)	

OT, Olfactory Training; OL, Olfactory Loss; TDI, Threshold, Discrimination, Identification. [a] Comparison by t test or chi-square test, as applicable.

[27]. An increase in orthonasal identification score and TDI score of at least 3 and 5.5 points, respectively, was considered as clinically significant [30].

Retronasal olfactory function

Retronasal olfactory function was tested using 20 powdered tasteless aromas (Givaudan Schweiz AG, Dubendorf, Switzerland) as described by Yoshino et al. [31]. For each trial, participants were blindfolded and occluded their nostrils before delivering each stimulus, in powdered form (approximately 0.05 g), to the mid-dorsal section of the participant's anterior tongue. The tongue was withdrawn into the mouth, the nostrils were unblocked, and participants then exhaled through their nostrils. After exhalation, participants identified the odour from a list of four verbal descriptors. The total score ranged between 0 and 20 and was based on the sum of correctly identified flavours. A compromised retronasal smell was defined as a score <12 [32]. Although a validated cut-off has not been determined for this olfactory modality, an increase of 4 or more points in the total score was considered indicative of a clinically relevant improvement in retronasal olfactory function. This cut-off value was chosen by analogy with the 3 points established for orthonasal olfaction, considering the similarity between the two olfactory modalities evaluated.

Statistical analysis

For statistical analyses, SPSS (Statistical Packages for Social Sciences, version 29.0, SPSS Inc., Chicago, IL, USA) was used. Standard descriptive statistics were used to characterise the study sample. Comparisons between groups were performed using t test for independent samples and a chi-square test. The intervention effect was estimated effect as absolute differences before and after the intervention, with corresponding 95% confidence intervals (CIs).

Results

Among the 114 enrolled participants, the mean (SD) age was 48 (13) years, and 73 patients (64%) were female (Table 1). The mean (SD) duration of OL at the time of enrolment was 9.5 (3.7) months, and 72 patients (63%) reported concurrent symptoms of phantosmia or parosmia. The self-reported olfactory function on the VAS-score at enrolment had a mean (SD) score of 35 (25.0). The mean (SD) TDI score at enrolment was 22.6 (6.0) points. A total of 68 participants (60%) were adherent to the

Table 2. Change in olfactory function according with adherence to OT.

	All			Adherent to OT protocol			Not adherent to OT protocol		
	Mean (95% CI)		Post- to pre-OT mean difference (95% CI)	Mean (95% CI)		Post- to pre-OT mean difference (95% CI)	Mean (95% CI)		Pre- to post-OT mean difference (95% CI)
	Pre-OT	Post-OT		Pre-OT	Post-OT		Baseline	Post-OT	
VAS olfaction, mm	35 (30 to 40)	54 (48 to 61)	19 (15 to 24)	35 (29 to 41)	62 (54 to 71)	27 (21 to 34)	36 (28 to 43)	43 (34 to 52)	7 (5 to 9)
TDI score	22.6 (21.5 to 23.7)	27.3 (26.1 to 28.4)	4.6 (3.8 to 5.4)	22.2 (20.6 to 23.7)	28.2 (26.6 to 29.7)	6.0 (5.0 to 7.0)	23.3 (21.7 to 24.9)	25.9 (24.2 to 27.7)	2.6 (1.5 to 3.7)
orthonasal threshold score	4.3 (3.9 to 4.8)	5.9 (5.3 to 6.5)	1.5 (1.1 to 2.0)	4.3 (3.7 to 5.0)	6.3 (5.6 to 7.1)	2.0 (1.3 to 2.7)	4.3 (3.7 to 4.9)	5.2 (4.4 to 5.9)	0.9 (0.2 to 1.5)
orthonasal discrimination score	8.7 (8.3 to 9.2)	10.7 (10.3 to 11.1)	2.0 (1.6 to 2.4)	8.5 (7.9 to 9.1)	10.9 (10.3 to 11.5)	2.4 (1.9 to 2.8)	9.1 (8.5 to 9.7)	10.4 (9.8 to 11.1)	1.3 (0.7 to 1.9)
orthonasal identification score	9.6 (9.0 to 10.1)	10.7 (10.2 to 11.2)	1.1 (0.7 to 1.5)	9.3 (8.5 to 10.1)	11.0 (10.2 to 11.7)	1.6 (1.1 to 2.2)	9.9 (9.1 to 10.7)	10.3 (9.6 to 11.1)	0.4 (-0.1 to 0.9)
Retronasal identification score	11.3 (10.6 to 11.9)	13.6 (12.9 to 14.4)	2.4 (1.8 to 2.9)	11.1 (10.1 to 12.1)	13.8 (12.8 to 14.7)	2.6 (1.9 to 3.4)	11.5 (10.6 to 12.4)	13.5 (12.5 to 14.5)	2.0 (1.3 to 2.7)

OT, Olfactory Training; TDI, Threshold, Discrimination, Identification.

intervention protocol. At baseline, VAS olfaction and the TDI score were slightly better in the non-adherent group than to the adherent group, but the difference was not statistically significant.

Changes in olfactory function according to adherence to olfactory training are reported in Table 2. Overall, the mean (95% CI) increase in TDI score was 4.6 (3.8 to 5.4). The increase in TDI score was more evident in patients who optimally adhered to the protocol than those did not (Figure 1A) The TDI score increased from 22.2 to 28.2 in the group that optimally adhered to the olfactory training (mean increase: 6.0; 95% CI: 5.0-7.0 – Table 2), and from 23.3 to 25.9 in the group that did not adhere to the olfactory training (mean increase: 2.6; 95% CI: 1.5-3.7), with a mean difference of 3.4 (95% CI, 1.9 to 4.9). Among those who adhered to the intervention protocol, the mean (95% CI) increase in the orthonasal threshold score was 2.0 (1.3-2.7), compared to 0.9 (0.2-1.5) among those who did not adhere, with a mean difference of 1.1 (0.1-2.0). The mean (95% CI) increase in the orthonasal discrimination score was 2.4 (1.9-2.8) among adherents, while it was 1.3 (0.7-1.9) among non-adherents, with a mean difference of 1.1 (0.3-1.9). Regarding the orthonasal identification score, the mean (95% CI) increase was 1.6 (1.1-2.2) among adherents and 0.4 (-0.1-0.9) among non-adherents, with a mean difference of 1.2 (0.5-1.9). Finally, the increase in retronasal identification score was less marked than in TDI score (Figure 1B): the mean (95% CI) increase in the retronasal identification score was 2.6 (1.9-3.4) among adherents and 2.0 (1.3-2.7) among non-adherents, with a mean difference of 0.6 (-0.4-1.7).

On an individual basis, subjects experiencing a clinically significant increase in TDI score (≥ 5.5) were 39 (57%) and 10 (22%) in the adherent and non-adherent group, respectively (absolute difference, 35%; 95% CI, 18% to 51%) (Figure 2A and Table 3). This was associated with a greater perception of subjective improvement (absolute difference in mean VAS score improvement, 20; 95% CI, 13 to 28) by patients adhering to the training (Table 2). Among participants with a baseline score ≤ 13, subjects experiencing a clinically significant increase in orthonasal identification score (≥ 3 points) were 26 (41%) and 5 (11%) in the adherent and non-adherent group, respectively (absolute difference, 30%; 95% CI, 15% to 45%) (Table 3). Among participants with a baseline score ≤ 16, subjects experiencing a clinically significant increase in retronasal identification (≥ 4 points) were 35 (56%) and 7 (16%) in the adherent and non-adherent group, respectively (absolute difference, 40%; 95% CI, 24% to 56%) (Figure 2B and Table 3).

Discussion

This prospective observational study demonstrates that adhe-

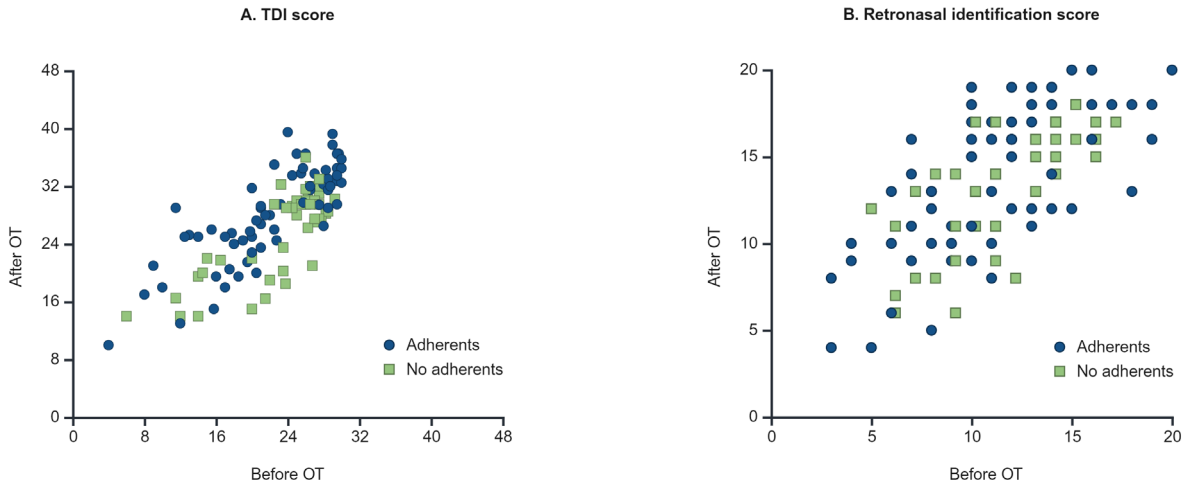

Figure 1. Scatter plot comparing TDI score (A.) and retronasal score (B.) before and after olfactory training. OT, Olfactory Training; TDI, Threshold, Discrimination, Identification.

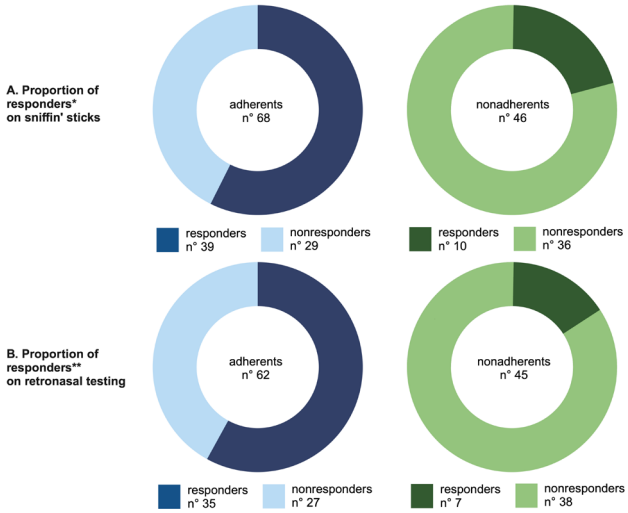

Figure 2. Proportion of responders by adherence to olfactory training. (A.) Proportion of responders* on sniffin' sticks (B.) Proportion of responders** on retronasal testing among participants with a baseline score ≤ 16. * Responders, defined as subjects experiencing a 5.5-point change or greater on the TDI score. **Responders, defined as subjects experiencing a 4-point change or greater on the retronasal identification score.

rence to OT over a 4-month period is associated with clinically significant improvements in both orthonasal and retronasal olfactory function among individuals with persistent post-COVID-19 OL. The improvements were substantially larger in the adherent group than the non-adherent group across multiple olfactory outcome measures.

The mean increase of 6.0 points in the composite TDI score for the adherent group exceeded the established threshold of 5.5 points for a clinically relevant improvement in the Sniffin' Sticks test battery [30]. Over half (57%) of adherent participants experienced such a clinically meaningful increase in their TDI scores. This compares favourably to previous OT studies in post-COVID-19 olfactory dysfunction, which have reported more modest impacts potentially attributable to suboptimal adherence rates [33].

Importantly, we observed improvements not only in the standard orthonasal olfactory testing, but also in assessments of retronasal olfactory function which contributes substantially to flavour perception during eating and drinking [34]. 56% of adherent participants had a clinically relevant increase of 4 or more points in their retronasal odour identification scores. This suggests that OT can help restore the full multi-modal olfactory experience encompassing both orthonasal and retronasal pathways. However, the minimal clinically important difference cut-off of the retronasal olfactory test is critical for the evaluation of the significance of the changes. Because it can be calculated by several methods [35], future research on larger datasets is needed to reassess the practical value of the currently used approach. At the same time, the results based on the presently used approach should be viewed with caution.

A critical challenge moving forward is to identify approaches that can maximize adherence rates and bolster the efficacy of OT interventions. A recent study found that a substantial number of patients with OL prematurely discontinued OT due to a perceived lack of improvement in their olfactory function [33]. Notably, those who discontinued OT because of a subjective perception of limited benefits exhibited poorer olfactory outcomes at follow-up than individuals who persisted with the training regimen confirming data observed in our investigation. These findings highlight the importance of emphasizing

Table 3. Clinically significant improvement in ortho- and retronasal olfactory function according with adherence to OT.

	Participants, No. (%)							
	All		Adherent to OT protocol		Not adherent to OT protocol		Absolute difference (95% CI)	p-value [a]
Post- to pre-OT TDI score								
< 5.5	65	(57)	29	(43)	36	(78)		<.001
≥ 5.5	49	(49)	39	(57)	10	(22)	35 (18 to 51)	
Post- to pre-OT orthonasal identification score [b]								
< 3	78	(72)	37	(59)	41	(89)		<.001
≥ 3	31	(28)	26	(41)	5	(11)	30 (15 to 45)	
Post- to pre-OT retronasal identification score [c]								
< 4	65	(61)	27	(44)	38	(84)		<.001
≥ 4	42	(39)	35	(56)	7	(16)	40 (24 to 56)	

OT, Olfactory Training; TDI, Threshold, Discrimination, Identification. [a] Comparison by chi-square test. [b] Including subjects with a baseline orthonasal identification score ≤ 13. [c] Including subjects with a baseline retronasal identification score ≤ 16.

consistent adherence to OT, irrespective of patients' subjective perceptions of progress, as premature discontinuation may hinder potential therapeutic benefits. In our study, 60% of participants met the criteria for adequate adherence over the 4-month training period. While not optimal, this adherence was reasonably satisfactory compared to previous studies [33]. This could potentially be attributed to the counselling provided to participants emphasizing the importance of consistent training irrespective of subjective perceptions of improvement, coupled with monthly phone calls aimed at sustaining adherence. Such regular interactions and motivational support may have played a role in promoting adherence by reinforcing the rationale for persisting with the training regimen despite any perceived lack of progress.

Innovative strategies utilising principles from behavioural science, such as embedding training into existing daily routines, gamifying the experience through app-based delivery, or providing motivational interviewing could help sustain long-term adherence to OT. However, at the same time, such routines in addition to the sniffing should be kept to a certain minimum to not distract too much from the sniffing task [13]. The introduction of an OT ball (OTB) was found to improve adherence to OT and olfactory outcomes in patients with post-infectious olfactory dysfunction compared to classical OT [26]. After 12 weeks of training, the OTB group had significantly higher odour discrimination and composite TDI scores than the classical OT group. Tailoring the odorant exposures to individual preferences rather than using a standardized set of odours may also enhance adherence [21].

While most adherent participants derived benefit from OT, it is noteworthy that around 40% did not experience clinically significant TDI improvements after the 4-month regimen. For this subgroup of patients who remain refractory despite adequate adherence, it may be advisable to pursue an additional cycle of OT or to explore alternative therapeutic approaches. Although several researchers have explored modifications in the classical OT protocol such as using higher concentrations of odours, varying the sets of odours, or switching the sets of odours every few months [36–38], the classical OT protocol [14] remains the standard reference [8]. Combining OT with visual stimulations could amplify neural plasticity mechanisms [39,40]. A recent randomized clinical trial aimed to evaluate the efficacy of bimodal visual-OT and patient-preferred scents vs unimodal OT and physician-assigned scents in COVID-19 OL, found no clinically meaningful difference in olfaction, as measured by the University of Pennsylvania Smell Identification Test (UPSIT) score [21]. However, when examining within-patient changes in UPSIT scores and self-reported improvements, the active interventions showed greater improvements than the controls, with bimodal intervention potentially offering an added benefit. Thus, there remains a need to explore innovative strategies, such as incorporating visual elements or tailoring to patient-preferred odours, to maximize patient adherence and the effectiveness of OT interventions.

The biological mechanisms underpinning the therapeutic effects of OT likely involve enhancing neural regeneration and plasticity in both the peripheral olfactory epithelium and central olfactory circuits [13]. Repeated exposures to odours may upregu-

late the expression of olfactory receptors, neurotrophic factors, and genes involved in neurogenesis [41,42]. There is evidence that OT can lead to an increase in grey matter volume in primary olfactory regions and may improve functional connectivity within the olfactory brain network [43,44]. However, further research integrating psychophysical testing with molecular and cellular analyses is needed to fully elucidate these mechanisms.

A key strength of our study is the comprehensive psychophysical assessment of multiple olfactory domains using validated testing batteries. Furthermore, our operational definition of adherence based on participants' training diaries provides an objective measure grounded in their real-world intervention engagement. Potential limitations include the single-centre design and the lack of a randomized untrained control group, which may limit the generalizability of our findings. However, the significantly larger improvements in the adherent versus non-adherent groups suggest that the benefits cannot be solely attributed to spontaneous recovery over time. Future multicentre randomized controlled trials are warranted to confirm and extend these results.

Conclusion

This study provides compelling evidence that consistent adherence to a 4-month OT regimen can yield clinically meaningful improvements in both orthonasal and retronasal olfactory function among individuals with persistent post-COVID-19 olfactory deficits. These findings underscore the therapeutic potential of harnessing the neuroplastic capacity of the olfactory system through guided sensory stimulation. OT represents an accessible and low-risk intervention that should be considered for inclusion in multidisciplinary management strategies aiming to ameliorate the chronic and debilitating manifestations of long COVID-19. However, whenever OT is considered, participants/patients should be informed in detail about the effects of adherence to OT.

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Authors' contributions

PBR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design: PBR, TH, AMe, GT; Acquisition of data: PBR, FU, LB; Analysis and interpretation of data: All authors; Drafting of the manuscript: PBR; Critical revision of the manuscript for important intellectual content: PBR, TH, AMe, AMa, GT; Statistical analysis: PBR; Supervision: TH.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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