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Functional but Not Structural Brain Changes After Olfactory Training in Women With COVID-19-Associated Olfactory Dysfunction

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ABSTRACT

Background: Olfactory training (OT) is a recommended treatment for olfactory loss and has proven effective in clinical contexts, yet its effects on the central-nervous system remain unclear. This study aimed to investigate the functional and structural brain changes in patients with post-viral olfactory loss undergoing OT.

Methods: Twenty patients with post-viral olfactory loss and 19 healthy controls underwent OT for 3 months. All participants were assessed using the Sniffin' Sticks test and magnetic resonance imaging (MRI). Voxel-based morphometry and olfactory bulb volumetry were performed on structural images. Presenting an unpleasant odor, n-butanol, in a canonical block design, functional MRI was performed using whole-brain and region of interest analyses.

Results: Patients with post-viral olfactory loss showed significant improvement following OT. Enhanced functional activations were observed in the orbitofrontal cortex and parahippocampus, while OT had little or no effects on brain structures.

Conclusion: The present findings suggest that OT provides early perceptual and functional benefits, with structural changes potentially emerging later with extended training duration.

Level of Evidence: 2.

1 | Introduction

Olfactory training (OT), which involves repetitive exposure to specific odorous stimuli, is a cost-effective treatment for patients with olfactory dysfunction and has been shown to benefit even individuals with a normal sense of smell [1–4]. In clinical settings, OT is recommended for post-viral olfactory loss in general and specifically for COVID-19-associated olfactory dysfunction (C19OD) [5]. While extensive research has demonstrated the behavioral improvements associated with OT, studies examining its impact on brain changes remain limited.

Prior studies on OT have explored both structural and functional changes in the brain [6–8]. For instance, Han and colleagues found enlarged gray matter (GM) volume in the cerebellum, medial orbitofrontal cortex, and thalamus in patients with idiopathic olfactory loss after OT [9]. A similar increase in GM volume was observed in patients with post-infectious olfactory loss [10]. In a functional magnetic resonance imaging (fMRI) study

on patients with post-traumatic olfactory loss, OT was associated with increased activation in the right superior frontal gyrus [11]. Additionally, a study on post-viral olfactory loss found enhanced connectivity in areas involved in olfactory processing following OT [12]. Generally, patients in these studies had long-standing olfactory loss (> 2 years, except [12]). Intervals between the sessions were variable. Moreover, most previous studies only conducted a single scan for the control group and did not include OT for these participants, which is a significant limitation for the detection of potential training effects.

Given the lack of studies that have investigated both functional and structural brain changes in individuals with post-viral olfactory dysfunction following OT, we aimed to fill this gap. We hypothesized that OT could improve both neural function and structure related to olfaction by enhancing neural plasticity and recovery. This study comprehensively investigates the effects of OT on brain structure and function in patients with post-viral, particularly C19OD.

2 | Methods

2.1 | Participants

Twenty female patients with C19OD (mean age ± sd = 52 ± 7 years, mean duration ± sd = 22.4 ± 13.4 months, range 5–48) were recruited from August 2023 to July 2024. All participants experienced perceived OD from more than 3 months since the time of diagnosed SARS-CoV-2 infection. Twenty healthy participants were enrolled, with some data of one healthy participant missing for technical reasons, resulting in 19 of them (mean age ± sd = 45 ± 9) included in the final analyses. Inclusion criteria were: (1) Female gender (in order to avoid a possible effect of gender [13]); (2) Age: ≥ 18 years; (3) Patients should have C19OD; (4) Healthy individuals should not have had C19OD at any time. Exclusion criteria were (1) Lack of capacity to consent; (2) Pregnancy and breastfeeding; (3) Significant health impairments (e.g., uncontrolled diabetes mellitus, Parkinson's disease, significant renal insufficiency), which can be associated with disorders of olfactory function; (4) Acute or chronic inflammation of the nasal cavity; (5) MRI-specific exclusion criteria (e.g., metallic implants, pacemakers, intrauterine spiral).

All participants received detailed written and oral information and provided written informed consent. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden (BO-EK-318072022).

2.2 | Measures

2.2.1 | Sniffin' Sticks Test

Olfactory function was evaluated using the Sniffin' Sticks Test (SST), a validated assessment composed of three subtests: odor threshold, discrimination, and identification [14]. The threshold test included 48 pens, 16 containing phenyl ethyl alcohol (PEA) at varying concentrations, with participants identifying the scented pen among odorless pairs. The discrimination test required participants to identify the unique odor in sets of three, while the identification test involved recognition of common scents from a list of options. The TDI (Threshold-Discrimination-Identification) score, summing the subtest scores, ranged from 1 to 48, with higher scores indicating better olfactory function [15].

2.2.2 | Olfactory Training

Figure 1 illustrates the procedure of the current study. Both patients and controls were given four brown glass jars, each containing 3 mL of one of four different odors (phenyl ethyl alcohol for rose, product number: 77861; eucalyptol for eucalyptus, C80601; citronellal for lemon, 814,575; eugenol for cloves, W246719; Sigma, Taufkirchen, Germany), soaked in cotton

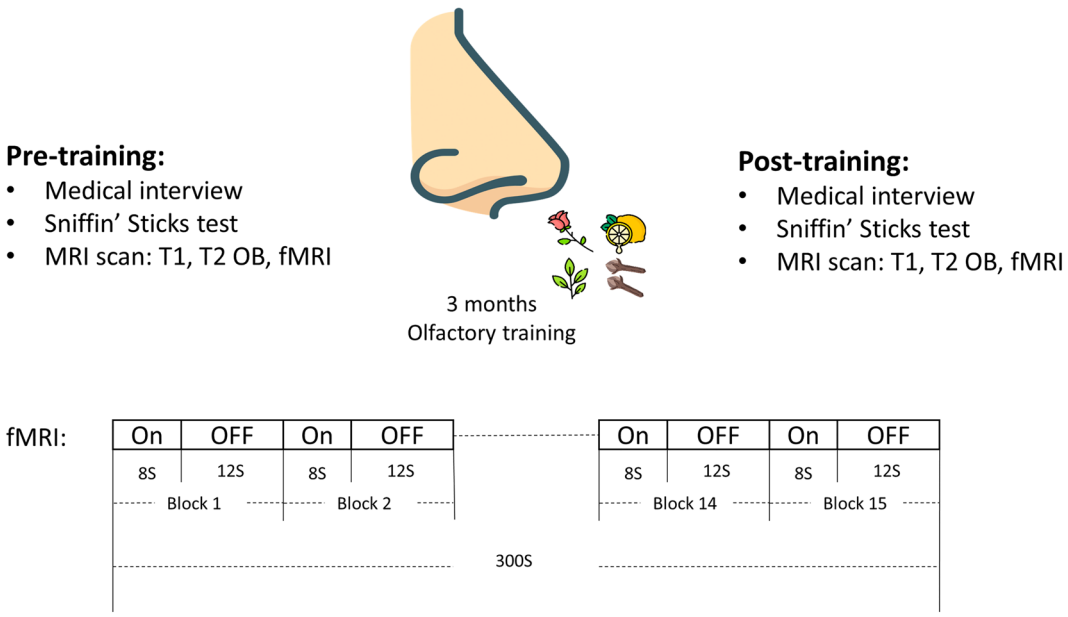

FIGURE 1 | Procedure of the current study in both control and patients with olfactory dysfunction cohorts. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com].

pads (Fuhrmann, Much, Germany; reference number: 40709). They were instructed to sniff each odor for approximately 20 s, both in the morning and evening for 3 months. Adherence to the training was asked with 4 questions in visit 2 using an adherence scale.

2.2.3 | MRI Protocol

A 3-Tesla MRI scanner (Siemens MAGNETOM Prisma, Forchheim, Germany) with a 32-channel head coil was used for image acquisition. T1 images were acquired using a 3D magnetization prepared gradient rapid acquisition gradient echo (MPRAGE) sequence with repetition time (TR) = 2300 ms, echo time (TE) = 3.43 ms, field of view (FOV) = 256 × 256 mm [2], and voxel size 1 × 1 × 1 mm [3]. Images of olfactory bulbs (OB) were collected using a coronal T2 single-shot echo-planar imaging (EPI) sequence with the following parameters: TR = 1000 ms, TE = 127 ms, flip angle = 100°, voxel size = 0.5 × 0.5 × 0.5 mm [3], slice thickness = 0.5 mm; FOV = 160 × 160 mm [2].

Each individual had 300 functional images collected with the parameters below: TR = 1000 ms, TE = 37 ms, flip angle = 52°, voxel size = 2 × 2 × 2 mm [3], slice thickness = 2 mm; FOV = 208 × 208 mm [2], with multiband factor = 8.

2.2.4 | Block Design in fMRI

N-butanol (Sigma, order number: 101543207; 5 mL) soaked in a cotton pad was selected for fMRI scanning. This was delivered birhinally using Teflon tubing connected to a portable computer-controlled olfactometer (Sniff-O, Cynexo, Udine, Italy, http://www.cynexo.com [16]). Odorous stimuli were embedded in a 2 L/min constant airflow. Stimuli were presented in a block design format, alternating between 8-s "ON" (odor) and 12-s "OFF" (odorless air) blocks. Following each odor presentation, participants rated the perceived intensity, pleasantness, and familiarity of the odor through an intercom system.

2.2.5 | Image Preprocessing

MRI images were pre-processed and analyzed using SPM12 (Statistical Parametric Mapping, UCL, London, UK) implemented in MATLAB (Version 2024a for Windows; The Mathworks Inc. Natick, MA, USA). The pre-processing steps were oriented by the default settings in SPM12 and included realignment and unwarping, slice timing, co-registration of functional with anatomical T1 images, segmentation based on the Tissue Probability Maps, normalization to the Montreal Neurological Institute space, and smoothing of functional images with a Gaussian kernel of $8 \times 8 \times 8\,mm^3$ full width at half maximum.

2.2.6 | fMRI Data Analyses

Functional data analysis employed a two-level restricted maximum likelihood approach. To better capture olfactory BOLD signal, the initial 2 s of ON and OFF sessions were excluded, yielding 6 s of ON and 10 s of OFF data for analysis. Paired t-tests examined pre- and post-training differences, while repeated measures analysis of covariance (rm-ANCOVA) assessed the time effect and group and time interactions, with age as a covariate. ROI analyses were conducted in Marsbar (https://marsbar-toolbox.github.io/) and analyzed using rm-ANCOVA in IBM SPSS version 29.0 (Chicago, IL, USA), and activations were reported in Montreal Neurological Institute (MNI) coordinates. Results were reported at uncorrected $p < 0.001$.

2.2.7 | OB Volume Measurement

The segmentation of the OB was performed using ITK-SNAP (http://www.itksnap.org) to process T2-weighted images. Two observers (ZL, JG) manually outlined the OB on each slice to obtain bilateral volumes, which were then summed and multiplied by the slice thickness to calculate the total volume. Measurements were averaged if the volume discrepancy was less than 10%; otherwise, the third observer (XX) performed an additional measurement. Final OB volumes were computed by averaging the two most concordant measurements [17].

2.2.8 | Voxel-Based Morphometry

Voxel-based morphometry (VBM) analyses were performed using the CAT12 toolbox (https://neuro-jena.github.io/cat//) implemented through SPM12 in MATLAB [18]. T1 images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF). Images were smoothed with a Gaussian kernel (full width at half-maximum 6 × 6 × 6 mm [3]). The following analyses were conducted: (1) *t*-test (pre- vs. post-training) in both control and patient groups; (2) *F*-test in a flexible factorial model to analyze the interaction effect of group × time. All results are reported at uncorrected $p < 0.001$.

2.2.9 | Statistical Analyses

Statistical analyses were performed using IBM SPSS version 29.0 (Chicago, IL, USA). Independent *t*-tests were applied to examine age differences in patient and control groups. The effect of OT on changes in olfactory function was analyzed with rm-ANCOVA, with "group" (patients vs. control) and "time" (pre- vs. post-training) as factors, controlling for age. For OB volume analysis, the right and left OB volumes were calculated separately using a similar rm-ANCOVA with age included as a covariate. Pearson correlation analysis was conducted to explore the relationship between the duration of olfactory loss, changes (post-pre) in olfactory scores, and selected ROI values. Two tailed $p < 0.05$ denoted significance.

3 | Results

3.1 | Behavioral Results

Age was significantly different between groups, where patients were older than controls ($t(38) = 2.85$, $p = 0.007$, see Table 1). Patients had significantly reduced olfactory function based on

TABLE 1 | Descriptive information (mean ± SD) and results of repeated measures ANCOVA using age as a covariate in patients and controls after olfactory training.

	Patients ($n = 20$)					Controls ($n = 19$)	t	p
Age (years)	51.55 ± 6.57					44.60 ± 8.73	2.85	**0.007**
Olfactory loss duration (months)	22.4 ± 13.4							
	Pre	**Post**	**Pre**	**Post**	$F_{interaction}$	p	***Contrast***	
TDI total	18.61 ± 8.25	23.74 ± 8.21	35.80 ± 3.78	37.32 ± 3.61	4.59	**0.039**	Patients < controls; patient: post > pre	
Threshold	2.56 ± 2.21	5.34 ± 2.80	8.64 ± 2.46	9.48 ± 3.20	4.93	**0.033**	Patients < controls; patient: post > pre	
Discrimination	8.20 ± 3.65	10.15 ± 3.12	13.79 ± 1.51	14.26 ± 1.41	1.34	0.26		
Identification	7.75 ± 4.45	8.30 ± 3.80	13.37 ± 1.46	13.58 ± 1.22	0.1	0.76		
Butanol intensity	3.84 ± 3.30	5.79 ± 3.22	6.61 ± 2.12	8.44 ± 1.34	1.23	0.4		
Butanol pleasantness	−0.74 ± 2.75	−0.53 ± 3.13	−0.44 ± 2.81	−0.53 ± 3.13	1.52	0.23		
Left OB volume	49.56 ± 13.04	51.90 ± 11.09	60.18 ± 15.90	58.40 ± 21.04	0.43	0.84		
Right OB volume	51.13 ± 11.32	52.05 ± 11.66	62.29 ± 15.17	63.86 ± 17.29	0.4	0.84		

Note: Bold indicates statistically significant values.
Abbreviations: OB = olfactory bulbs; TDI = threshold-discrimination-identification total score.

TDI total and subtest scores. During scans, they rated butanol as less intense compared with controls (all $p < 0.001$). Results from rm-ANCOVA controlling age suggested a significant interaction effect of TDI total score between time and group (F [1, 36] = 4.59, $p = 0.039$, Figure 2). Bonferroni corrected post hoc analysis indicated that this improvement was only significant for the patients' group (18.61 mean TDI pre-OT increased to 23.74 post-OT, $p < 0.001$). Regarding olfactory subtests this interaction effect was mainly seen in odor thresholds (F [1, 36] = 4.93, $p = 0.033$), but not for discrimination and identification (both $p > 0.05$). Following OT, both groups tended to rate butanol more intense in the scan (Time main effect: F [1, 34] = 3.01, $p = 0.092$), with no difference in pleasantness ratings ($p > 0.05$).

3.2 | fMRI Results From Whole Brain Analyses

For the interaction effect between group and time (contrast: [patient post—patient pre]—[control post—control pre]), the activations of the right medial OFC were increased in patients (peak: [12, 62, −14, k = 10], Figure 3). Moreover, for the time effect, the activation of the left and right parahippocampal cortex (peak: left: [−22, −20, −20, k = 10]; right: [20, −14, −22, k = 20]), and bilateral middle temporal gyrus were significantly higher after training (peak: left: [−56, −44, −4, k = 22]; right: [66, −46, 1, k = 22]) in both groups.

Paired *t*-tests with the contrast of post > pre-training in the patient group suggested that n-butanol activation was enhanced in the regions of the left inferior temporal gyrus (peak: [−38, −8, −34, k = 20]) and right fusiform (peak: [40, −6, −30, k = 21]). For controls, the activations of the right middle temporal gyrus (peak: [50, −24, −10, k = 123]), right superior frontal gyrus (peak: [24, 50, 16, k = 50]), left superior motor area (peak: [−10, 16, 56, k = 37]), and orbitofrontal cortex (OFC, peak: [16, 66, −44, k = 17]) were higher after training.

3.3 | ROIs Results

The OFC, both left and right parahippocampal gyrus, and bilateral middle temporal gyrus were chosen based on the whole brain analysis. A significant time effect (F [1, 36] = 5.39, $p = 0.026$) and a trend-significant interaction effect between group and time were found in the right parahippocampus (F [1, 36] = 3.68, $p = 0.063$). Post hoc analysis suggested only patients improved after OT compared to baseline activation (post-training > pre-training, $p = 0.006$). There was a trend towards significance for an effect of time in the left parahippocampus (F [1, 36] = 3.61, $p = 0.065$). The post hoc analysis suggested that more activation was present post-training compared to pre-training ($p = 0.015$). When looking into the post hoc analysis, even without a significant interaction effect, the higher activation in response to n-butanol only existed in patients (post-training > pre-training, $p = 0.012$). No other significant results were found (all $p > 0.05$).

Pearson's correlation results (see Table 2) showed that the change in OFC activation negatively correlated with the change in pleasantness (r [37] = −0.33, $p = 0.046$). Duration of olfactory

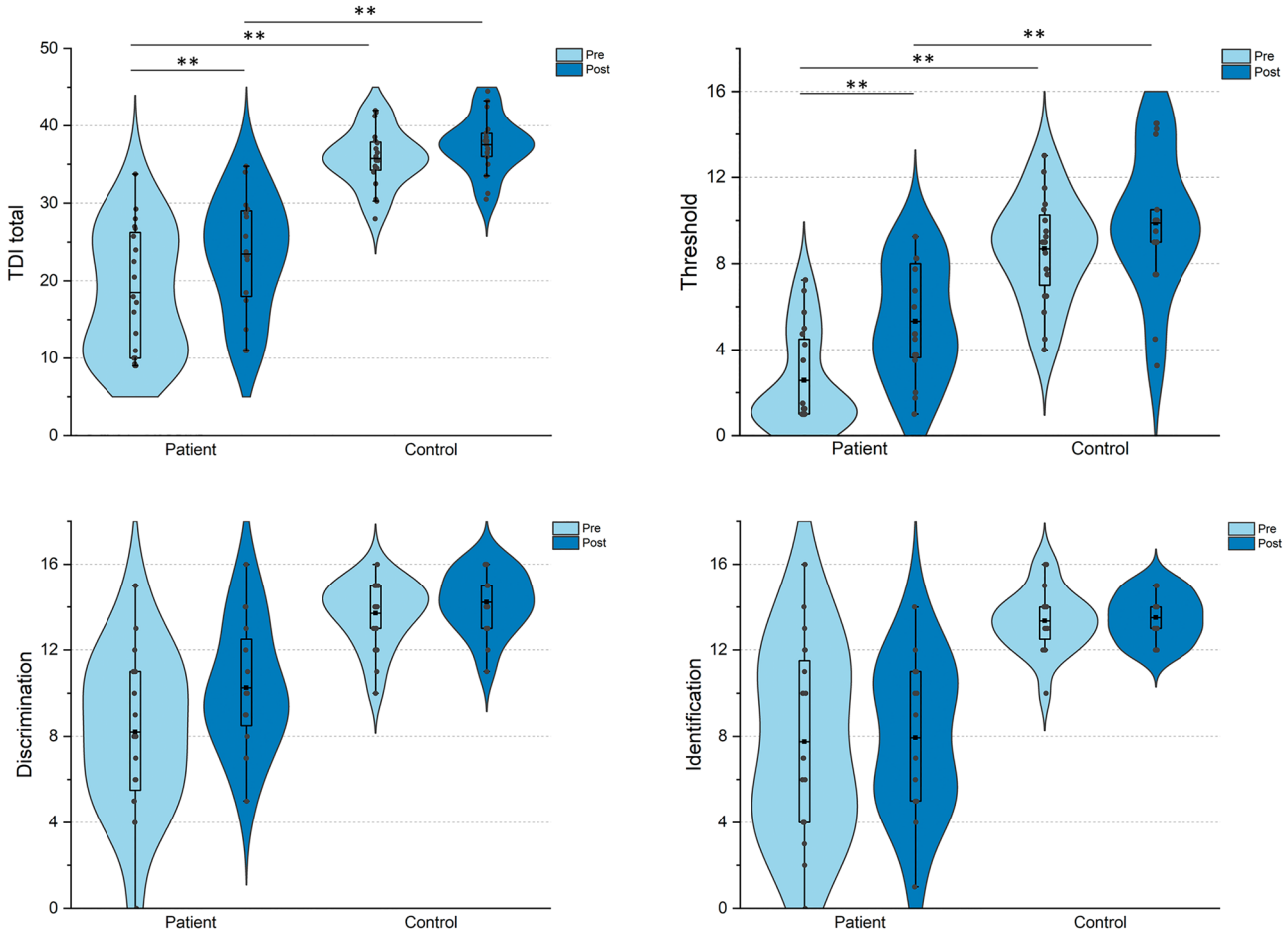

FIGURE 2 | Olfactory improvement in Sniffin' Stick tests after olfactory training in patients and controls. $^{**}p < 0.01$. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com].

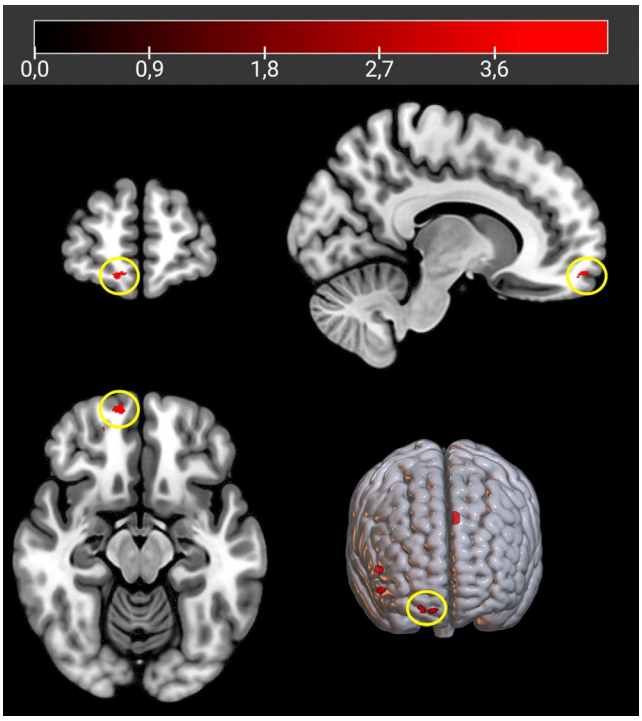

FIGURE 3 | Improved functional activation in the right orbitofrontal cortex from the whole brain analysis with significance level at uncorrected $p < 0.001$. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com].

loss positively correlated with change in discrimination (r [19] = 0.52, $p = 0.024$) and TDI scores (r [19] = 0.52, $p = 0.022$). The change in intensity of butanol positively correlated with the change in threshold (r [38] = 0.44, $p = 0.006$) and TDI scores (r [38] = 0.47, $p = 0.003$). The change in pleasantness negatively correlated with the change in discrimination scores (r [38] = −0.51, $p = 0.001$).

3.4 | VBM Results

Paired t-tests with the contrast of post-training more than pre-training in the patient group suggested that OT enlarged the GM volume in the regions of the right cerebellum (peak: [10, −54, −12, k = 23]). Similarly, for controls, the GM volume of the right cerebellum (peak: [8, −30, 33, k = 10]) was increased after training. There were no significant main effects or interaction effects in the F test (all $p > 0.05$).

3.5 | OB Measurement

Both left and right OB volumes of patients were lower compared to healthy controls before OT (left: t (37) = 2.29, $p = 0.014$; right: t (37) = 2.62, $p = 0.006$). The rm-ANCOVA suggested a main effect of time on the left OB (F [1, 36] = 5.22, $p = 0.028$), while the post hoc analysis suggested no difference

TABLE 2 | Correlation analysis results between changes in olfactory function, butanol intensity and pleasantness, and selected ROI values.

	T	D	I	TDI	Intensity	Pleasantness	OFC	Hippo_R	Tempo_L	Tempo_R	Hippo_L
T	1	0.007	−0.026	0.658**	**0.435****	0.223	−0.206	−0.020	−0.004	−0.050	0.196
D		1	0.184	0.576**	0.162	**−0.506****	0.141	−0.053	0.197	0.064	0.085
I			1	0.566**	0.199	−0.023	0.117	0.271	0.224	0.098	0.266
TDI				1	**0.471****	−0.109	−0.010	0.082	0.189	0.052	0.300
Intensity					1	−0.174	−0.018	0.311	−0.007	0.056	0.280
Pleasantness						1	**−0.330***	−0.031	0.024	−0.033	0.008
OFC							1	0.029	0.233	0.370*	0.188
Hippo_R								1	0.119	0.013	0.772**
Tempo_L									1	0.602**	0.166
Tempo_R										1	0.154
Hippo_L											1

Note: Bold indicates statistically significant values.
Abbreviations: D = discrimination, Hippo = hippocampus, I = identification, OFC = orbitofrontal cortex, T = threshold, Tempo = temporal gyrus.
*$p < 0.05$.
**$p < 0.01$.

($p = 0.83$). There was a trend-level significance of the group main effect on the right OB ($F [1, 36] = 3.89$, $p = 0.056$), with the post hoc analysis suggesting controls had a larger right OB volume than patients regardless of the time. There were no relationships between the change in OB volume and measured olfactory function or duration of olfactory loss. No other results were found (all $p > 0.05$).

4 | Discussion

The main findings of the present study are that in patients with C19OD: (1) OT significantly improved olfactory function; (2) OT was associated with enhanced functional activation in the OFC and parahippocampal region; (3) The change in OFC activation negatively correlated with the change in perceived pleasantness of butanol; (4) There were little or no structural changes in overall GM and OB volume before and after OT.

The present study demonstrates that OT facilitates olfactory improvement in patients with post-viral olfactory dysfunction. While controls who underwent OT showed some improvement (pre- vs. post-TDI total scores: 35.8 vs. 37.32), this change did not reach statistical significance. This finding aligns with previous research, which has consistently shown OT to be an effective treatment in clinical settings [2, 3, 19–21]. The potential mechanism underlying this benefit of training still remains unclear. A plausible explanation may involve neuroplasticity within the olfactory epithelium [22]. Systematic exposure to odorants may additionally stimulate basal cells, supporting neurogenesis, and the generation of olfactory receptor neurons, thereby enhancing olfactory function [2, 23]. Additionally, the improvement in the "top-down" processing of the olfactory system after OT may offer another explanatory mechanism for enhanced olfactory function [6, 11, 12]. The current study supports this idea, as there was increased post-OT functional activation in the OFC and parahippocampus—regions of the secondary olfactory cortex involved in complex olfactory processes such as odor coding and memory. In addition, the right hemispheric dominance is in line with previous studies suggesting a relatively higher significance of the right versus the left hemisphere in terms of olfactory functions [24, 25]. For instance, an early study presenting stimuli bilaterally found significant activation in the right OFC only [26]. Similarly, right hemisphere predominance has been documented in studies of odor memory [27, 28].

Correlational analyses revealed no significant relationships between the ROIs and improvements in olfactory function as assessed through odor threshold, discrimination, or identification. However, the change in OFC activation was negatively correlated with the perceived pleasantness of n-butanol, an unpleasant odor [29], suggesting that more pronounced unpleasantness indicates recovery of olfactory function. This finding is consistent with the observed behavioral improvements in olfactory function in the present study, indicating that OT contributes both behaviorally and functionally to olfactory improvement in patients with post-viral olfactory dysfunction. However, limited structural changes were observed in the current sample; only the GM volume of the cerebellum in both groups increased. The cerebellum is involved in olfactory processing and has been shown to be increased in previous research following OT [9, 10].

This increase might be associated with the increased frequency of sniffing the olfactory environment, which is organized to some degree in the cerebellum [30]. Clinically, the delayed appearance of structural changes following functional changes can be seen as positive in terms of recovery. In cases of short-term olfactory loss, the brain appears capable of relatively easy repair without the possible consequences of lasting structural alterations, which might be more challenging to compensate for in cases with a longer duration of olfactory loss.

Previous OT studies on patients with post-viral olfactory dysfunction have reported reorganized functional networks [6] or increased functional connectivity within olfactory-related networks [12]. However, these often involve small sample sizes and lack healthy control groups that undergo scanning after OT. Ideally, we would have manipulated three groups: patients with OT, patients without OT, and controls with OT, to allow for comparisons across different domains. Nevertheless, contrary to most previous studies [6, 10, 11], the present investigation included two scans for the controls, performed before and after OT. This allowed the present study to investigate the isolated effect of OT in individuals with and without olfactory dysfunction. One plausible explanation for the absence of structural changes could be that both patients and controls experienced structural improvements (in line with behavioral improvement), but these changes were too subtle to be detected within the relatively short training duration at the structural level. Additionally, given the close relationship between higher order olfactory tasks and cognition [31], the observed relationship between odor discrimination improvement and the change in pleasantness of butanol suggests that OT changes and improves the cognitive processing of olfactory stimuli [32]. Coupled with the enhanced functional activation in the parahippocampus and OFC, regions known to play key roles in cognition [33, 34], the absence of structural changes may indicate that OT initially promotes cognitive improvements, shown as increased functional activation, which appears to precede structural alterations at a central-nervous level [35–37]. Future studies should consider extending the OT duration and ideally include another patient group without training to distinguish the effects of spontaneous olfactory recovery from those induced by OT.

The inclusion of only female participants in this study may limit the generalizability of the findings. However, this approach was specifically chosen to reduce possible sources of variance which might influence the results. Specifically, gender is a factor that is relevant in olfactory-related fMRI research, with existing differences between men and women in brain function and activation patterns [13]. Independently of that, the large majority of studies report no gender differences in terms of recovery from olfactory loss in relation to OT [38, 39], which suggests that, while the brain activation patterns might differ between genders, the clinical outcomes of OT can likely apply to the patients in both genders.

There are some limitations to the present study. Firstly, the sample size is relatively small. However, we conducted two scans in both the control and patient groups, which provided additional information over time and the possibility to compare comprehensively using an F test model. Secondly, the age difference between participants could potentially confound the results. Although we applied statistical corrections using age as a covariate, future studies should aim to control for age differences during data collection.

5 | Conclusion

OT is associated with enhanced olfactory function and functional activation in the OFC and parahippocampus in female patients with C19OD, indicating consistent behavioral and central-nervous improvements following training. The lack of significant structural changes may be attributed to the relatively short duration of OT. This suggests that while cognitive and functional improvements occur relatively quickly, structural changes might emerge only over a longer period.

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Conflicts of Interest

The authors declare no conflicts of interest.

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