Web-application guided bimodal olfactory training for COVID-19 patients: a randomized trial

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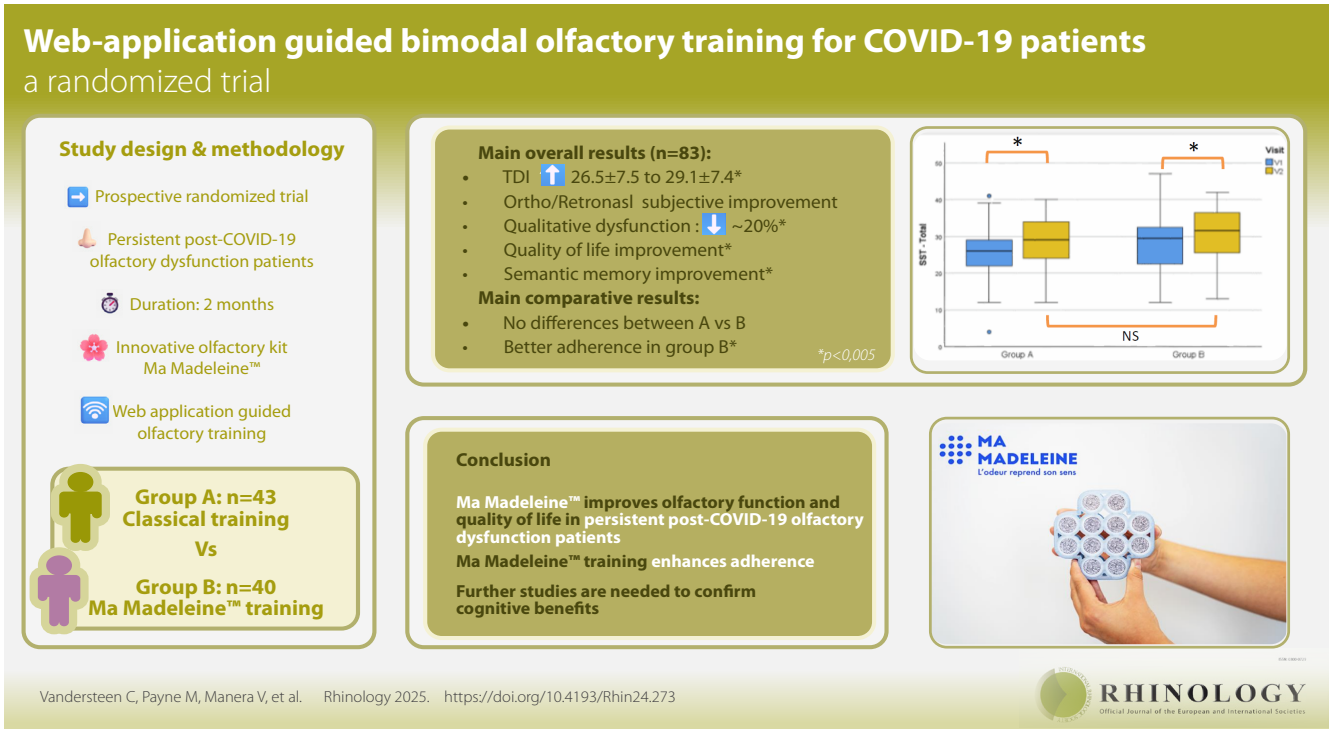

Abstract

Background: Many Post-Acute COVID-19 Syndrome (PACS) patients continue to experience persistent dysosmia up to two years post-pandemic. Cognitive and semantic memory functions, along with olfactory associative areas, may be affected in PACS without olfactory recovery. Visual-olfactory bimodal olfactory training may stimulate these areas. This study evaluates the olfactory recovery using a new bi-modal training kit, MaMadeleine™, assisted by a web application. **Methodology**: A prospective randomised study (Nov 2021–June 2022) included PACS patients aged ≥14 with post-infectious olfactory dysfunction. Patients were randomized for two months of simple (A) or semantic (B) visual-olfactory training. Evaluations included clinical assessments, Sniffin' Sticks Tests, and quality-of-life questionnaires. Adherence to treatment was monitored via the web application. **Results**: We included 83 patients, on average 13±5.6 months after COVID-19. Olfactory training using MaMadeleine™ led to subjective ortho- and retro-nasal olfactory improvement in 79.4% (n=58) and 58.9% (n=43) of patients, respectively, with Sniffin' Sticks Test scores increasing from 26.5±7.5 to 29.1±7.4. Both groups saw a 20% decrease in parosmia and phantosmia. No significant differences in recovery were observed between groups, although exploratory findings in a small subgroup (n=10) with semantic memory impairment suggest a possible benefit of bimodal training, warranting further investigation. Quality of life improved significantly in both groups. Adherence was better in group B than in group A. **Conclusions**: MaMadeleine™ training improves subjective olfactory function, psychophysical test results, and quality of life in PACS patients with olfactory dysfunction. Multimodal training enhances adherence. Further studies are needed in semantic memory-impaired patients.

Key words: COVID19, post-acute COVID syndrome, olfactory loss, visuo-olfactory, semantic memory

Introduction

According to public websites such as https://data.who.int/dashboards/covid19/cases, over 777 million people have contracted SARS-CoV-2, with up to 53% [1] experiencing acute olfactory loss. Among mild cases, 5% reported smell/taste changes at 3 years, with 92% [2] recovering. Two years post-infection, 3.5% (n=6/171) still had quantitative dysfunction, rising to 29.8% (n=51/171) when including qualitative distortions (parosmia, phantosmia)[3]. Olfactory training (OT) is the only validated treatment for post-viral olfactory loss. Pre-COVID-19, recovery rates ranged from 11–68% in 12–16 weeks and up to 56% in 6 months [4], with a Minimal Clinically Important Difference (MCID) ≥ 5.5 achieved in 60% to 70% of patients, depending on protocol duration [5]. For persistent olfactory dysfunction related to post-Acute COVID-19 Syndrome (PACS), results vary: some report symptom/test improvements [6], others none [7]. Extended OT (6–9 months) may reduce parosmia [8]. Prior work revealed recovery focused on threshold, not identification/discrimination [9]. PACS often impairs identification [10], which is cognitively demanding, suggesting central causes of persistent dysfunction.

Several authors have reported that bilateral stimulation of visual and olfactory modalities may enhance certain cognitive functions [11–13]. Pairing images with odours strengthens associations, aiding discrimination and identification [14]. Visual input adds context and boosts attention, adherence, and neuroplasticity [15]. Recent imaging shows increased connectivity in olfactory and visual cortices after short-term anosmia [16].
Considering the challenges related to neural connectivity, as well as the empirical limitations of conventional olfactory training—such as poor adherence, variability in rehabilitation materials (e.g. essential oils of inconsistent quality, origin, or authenticity, sometimes replaced by homemade kits), and issues with odour stability—we developed a novel approach to olfactory self-training. This method involves a high-quality olfactory kit paired with a newly designed web application, enabling both standard and bimodal visuo-olfactory training to reactivate olfactory sensations. We called it MaMadeleine™ (Utility Certificate N°FR2406301) in reference to Proustian moments recalling memories thanks to smell a specific odour. The aim of this study was to evaluate global OT efficiency of MaMadeleine™ in a pilot study comparing both type of OT supervision and to identify some predictive factors of this efficiency.

Materials and methods

The prospective randomized study was approved by the national ethics committee (N°2021-A01924-37). From November 2021 to June 2022, we enrolled patients aged 14 and older at the Olfaction Department, ENT Division, Nice University Hospital. All had confirmed COVID-19 (via RT-PCR or CT and serology) and reported persistent olfactory dysfunction in a PACS context. PACS, per the WHO Delphi consensus [17], includes symptoms starting from infection or within three months after, lasting over two months without other causes.

We excluded patients with pre-existing olfactory/gustatory dysfunction, sinonasal or neurological conditions, post-viral hyposmia/anosmia prior to COVID-19, or anatomical blockage of the olfactory cleft (nasofibroscopy). COVID-19 reinfection during the study also led to exclusion.
During the first evaluation (V1), we extracted patients' demographic data and clinical features, including subjective (presence or not of an ortho- or retro-nasal olfactory dysfunction, visual analogic scale of ortho-nasal olfactory function from 0% to 100%), nasofibroscopy (assessing nasal cavity patency and differential diagnosis), and evaluation of olfactory loss using Sniffin' Sticks Test® (SST) [18]. Olfactory perseverations, a recently described PACS symptom [19], were included as triggered, identifiable, often unpleasant perceptions persisting from several hours to several days without stimuli. Semantic memory was assessed via the Pyramid Palm Tree Test (PPTT), and quality of life using the French Short-QOD-NS [20]. Participants were randomised into simple (A) or semantic (B) OT groups using a computer-generated sequence. V2 evaluation occurred 2 months (± 2 weeks) after V1. The primary outcome was SST score change; secondary outcomes included subjective complaints, semantic performance, adherence, and quality of life.

Olfactory training kit

Instructions were given via a home-made web application that tracked patient connections and progression in the OT pipeline. Instructions varied by group randomization. Connection management was initiated during the face-to-face V1 session and handled remotely if any issues arose during the OT process. Adherence to treatment was monitored through daily connections to the web application. It was defined as the ratio of OT sessions correctly attended (monitored via daily session connections) to the total number of scheduled sessions (i.e. (X/120) x100 for Group A and (X/60) x100 for Group B, respectively). The olfactory training kit included 12 sorbarods filled with high-quality, pleasant, and concentrated fragrances (up to 10% dilution for better predictive effect) [21]. Fragrances were selected by our team and a French professional master perfumer: clean linen, lavander, cucumber, peach, green mint, cloves, pine, sea, banana and strawberry sweet "Arlequin", cut grass, anise, and eucalyptus. The fragrances were associated three by three according to their opposition on the word-cloud olfaction qualities [22]. Each trio thus form was presented for two weeks. Session 1: clean linen-lavender-cucumber, session 2: peach-green mint-cloves, session 3: pine, sea, banana and strawberry sweet "Arlequin", session 4: cut grass, anise, and eucalyptus. The opposition between each odor was starting from maximal (ses-

Figure 1. The MaMadeleine™ olfactory kit – 12 sorbarods filled with different selected fragrances are carried in a blue recycled plastic recipient allow patient to store efficiently the kit. Circular QRCODE are printed to get some mandatory information's. The pipeline is guided by a web-application reached by any internet-connected device.

sion 1) to minimal (session 4) according to Lincon et al. [22]. Each fragrance was associated with pictures and with specific words. First, we collected the words associated with each fragrance among a panel of 50 people (volunteers from the Speech and Language Department and workers from the Memory Research Center) and the pictures where then made according to this word corpus. The final choice of the twelves fragrances was determined by the quality and the duration of the odor when processed in sorbarods, and of by the number of possibilities of the words evocation and association as well as illustration. All sorbarods and the cross-supporting structure were 3D printed using recycled materials (Figure 1). Each sorbarod was tagged with a QR code adhering to International Fragrance Association (IFRA) standards and listed fragrance components per security and poison control center recommendations. A number was inscribed below each item rather than above, so that they could not be easily recognised immediately.

Group A: patients self-exposed to two random odours from the kit twice daily (up to 5 minutes each), 6 days/week for 2 months. Guided by the web app, they attempted blind recognition; if no scent was detected, a "no recognition" click triggered a picture and label (e.g. "Chocolate", "Cedar"), following Hummel's protocol [21], to improve re-identification. Visual stimulation was single-odour-centred and congruent.

Group B: Patients self-exposed to three selected odours from the kit according to the session organized from 1 to 4, once daily for 10 minutes (matching Group A's total daily exposure but in a single session), six days per week, for two months. Every two weeks, the session changed thereby covering all 12 odours. In each two-week block, the first week focused on olfactory identification without verbal or image labelling, based on the spontaneous association between the perceived fragrance and three pictures (only one picture was congruent, the two others being on a complete different quality field, such as: cucumber/bacon/cedar), on the perceived fragrance and ten words (i.e. Fresh, cucumber, bug, green, crunchy, Greek salad, beach, zest, mint, strawberry) and on the proximity of the perceived fragrance and three pictures (i.e. Tzatziki/coconut tree/strawberry). Then the second week introduced labels and images of the three odors and was structured according to the semantic feature analyses [23]. During this second week, classification exercises (semantic pairing according to odor attributes such as pleasant/unpleasant, sweet/sour, domestic/natural), semantic feature evocated (naming, designation, memories), and image association [24]. This approach integrates multiple semantically convergent types of stimuli [12] – such as colours, verbal cues and images – to enhance odour discrimination and identification. Some application-functioning screenshots illustrates these two groups in supplemental material (Figure S1 and S2).

Table 1. Demographics, clinical and olfactory comparison between groups at V1.

	Group A (N=43)		Group B (N=40)		p-value
	Mean	[SD]	Mean	[SD]	
Age	43,6	15,7	43,3	14,4	0,862
Self-subjective total quantitative ortho-nasal olfactory function (%)	29,2	20,8	33,1	27,0	0,778
Short-QOD-NS – Total score	11,0	5,1	10,6	5,4	0,744
SST scores	5,0	3,7	5,8	3,8	0,346
Threshold	9,9	2,9	10,7	2,4	0,257
Discrimination	10,2	2,8	11,5	2,8	**0,026**
Identification	25,1	7,4	28,0	7,4	0,060
TDI	N	%	N	%	p-value
Sex					**0,013**
Female	29	67,4	36	90,0	
Male	14	32,6	4	10,0	
Level of education					0,861
Primary level	2	4,7	1	2,5	
Secondary level	9	20,9	8	20,0	
Superior level	32	74,4	31	77,5	
Quantitative subjective persistent olfactory dysfunction					
Orthonasal	43	100	40	100	-
Retronasal	35	81,4	36	90	0,270
Qualitative subjective persistent olfactory dysfunction					
Olfactory perseverations	2	4,7	5	12,5	0,199
Parosmia	35	81,4	33	82,5	0,896
Phantosmia	16	37,2	11	27,5	0,345
SST classification*					**0,044**
Normosmic	7	16,3	16	40,0	
Hyposmic	31	72,1	22	55,0	
Anosmic	5	11,6	2	5,0	

[SD]=standard deviation; Short-QOD-NS = Short Questionnaire of olfactory disorders – negative statements; SST = Sniffin' Sticks Test.

Olfactory dysfunction assessments

The Sniffin' Sticks Test (SST) [18] assesses Threshold, Discrimination, and Identification. The composite TDI score defines normosmia SST≥30.75), hyposmia (16.25≥X≥30.5), and anosmia (≤16) [18]. Age- and sex-specific cut-offs apply ≥10th and <10th percentiles, respectively [18].

Semantic memory assessment

Semantic memory was assessed using the Pyramids and Palm Trees Test (PPTT), a validated word-matching task comprising 52 triads. Participants selected the semantically closest word to a target displayed above two options. Performance was age- and education-adjusted [25]. A Z-score below –1.65 (5th percentile) indicated impairment.

Olfactory quality of life

Olfactory-specific quality of life was assessed using the French validated Short-QOD-NS [20], derived from the negative items of the QOD. This seven-item questionnaire assesses social life, eating, anxiety, and annoyance (score range 0–21; higher scores = better quality of life). It is brief and minimally burdensome.

Sample size

The number of subjects was estimated through a power analysis based on the primary objective: comparing the pre–post intervention changes in TDI scores from the Sniffin' Sticks Test® (SST) between the simple (A) and semantic (B) OT groups. The minimal clinically significant difference (MCID) was set at 2 points. This threshold was determined based on unpublished internal pilot data from a pre-study sample of 20 PACS patients under-

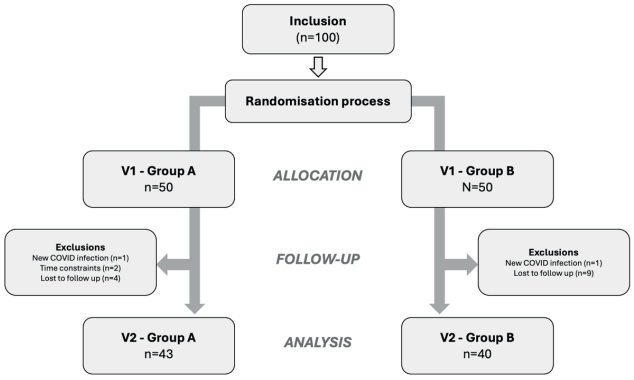

Figure 2. Study flowchart.

going olfactory training, in whom a change of ≥2 points in TDI was associated with a noticeable subjective improvement in olfactory perception. Although smaller than the traditionally cited MCID of 5.5 for general post-viral anosmia, this lower threshold reflects the narrower baseline distribution and higher TDI scores typically observed in PACS patients with long-term dysfunction. The standard deviation for the TDI score in our target population was estimated at ~3.0, yielding an effect size (Cohen's d) of 0.66. Using G*Power v3.1, a two-tailed t-test for independent samples ($\alpha = 0.05$, $\beta = 0.10$, power = 90%) indicated a required total sample size of 100 participants (50 per group).

Randomization

Randomisation used a computer-generated sequence with web-based allocation concealment. Physicians enrolled participants and remained blinded at follow-up

Statistical analysis

Due to non-normality (Shapiro-Wilks), Wilcoxon signed-rank tests assessed pre/post changes in quantitative variables (e.g., TDI). McNemar tests were used for binary changes (e.g., parosmia). Mann-Whitney compared groups (e.g., semantic vs non-semantic OT). Spearman's rho evaluated correlations (e.g., adherence vs TDI change). Significance was set at a two-tailed alpha of 0.05.

Results

We enrolled 100 PACS patients with persistent olfactory dysfunction (mean duration: 13 ± 5.6 months; mean age: 44 ± 15 years; 79.8% female; Table 1). Seventeen were excluded (13 lost to follow-up, 2 reinfected, 2 withdrew), as reported in the flowchart (Figure 2). At V1, mean subjective olfactory function was 31 ± 24%. Only 2 patients (2.4%) reported true taste loss while 71 (85.5%) reported subjective retro-nasal dysfunction. No olfactory cleft obstruction was found. Groups were comparable, except for sex distribution (p=0.013), severity of olfactory dysfunction, and baseline identification scores: Group B showed higher identification (p=0.026) and SST scores reflecting milder impairment (Table 1; p=0.044). Mean adherence was 78.5 ± 19.3% [18-100%], significantly higher in Group B (83.6%± 17.4%)) vs Group A (73.7% ± 19.8%, p = 0.010).

Results of olfactory training

Subjective total quantitative olfactory function improved in 79.4% (n=58) of patients, with 58.9% (n=43) reporting an improvement in both ortho-nasal and retro-nasal olfactory function. There was no significant difference between group A and group B in the proportion of patients reporting improved orthonasal olfactory function (70% [n=28] vs 76.9% [n=30], p=0.486) or improved retronasal olfactory function (50% [n=20] vs 59% [n=23], p=0.432). OPA significantly improved from V1 to V2 (see supplement table in supplemental content), as TDI went from 26.5±7.5 to 29.1±74.4 (p<0,001). This improvement occurred across all SST olfactory subdimensions (Threshold, Discrimination, Identification). The number of normosmic patients increased significantly from 23 (27.7%) to 39 (47%) (p=0.003), while there was a moderate decrease in anosmic patients. Parosmia and phantosmia also significantly improved (see supplement table in supplemental content). When comparing results between the two groups undergoing olfactory training (Table 2), no significant differences were found in subjective, qualitative or quantitative assessments at V2 vs V1, except for a higher frequency of patients in group A achieving improvement in TDI scores beyond the MCID compared to those in group B (respectively 41,8% [n=18] vs 20%[n=8)], p=0,032). Graphic representation of both groups OPA improvements is reported in Figure 3.
In a post-hoc analysis focusing on PPTT impaired patients (n=10; 12%), we observed a trend towards greater improvement in OPA for group B, particularly in the identification subdimension, although this trend did not reach statistical significance. Conversely, there was a significant worsening in the threshold subdimension observed more in group A (p=0.049).

Semantic memory results

PPTT scores improved overall from V1 to V2, with the proportion of semantic impaired patients decreasing significantly from 10 (12.2%) to 2 (2.4%) at V2 (p=0.008). However, there were no significant differences in ΔPPTT scores between group A and B at V2, with scores of 0.2±1.7 versus 0.6±1.7, respectively (p=0.584).

Quality of life results

Specific olfactory quality of life (Short-QOD-NS) improved significantly from V1 to V2, increasing from 11.2±5.2 to 12.8±5.8 (p<0.001). However, there were no significant differences in Δ score-Short-QOD-NS between group A and B at V2, with scores of 1.4±3.1 versus 1.7±3.6, respectively (p=0.781).

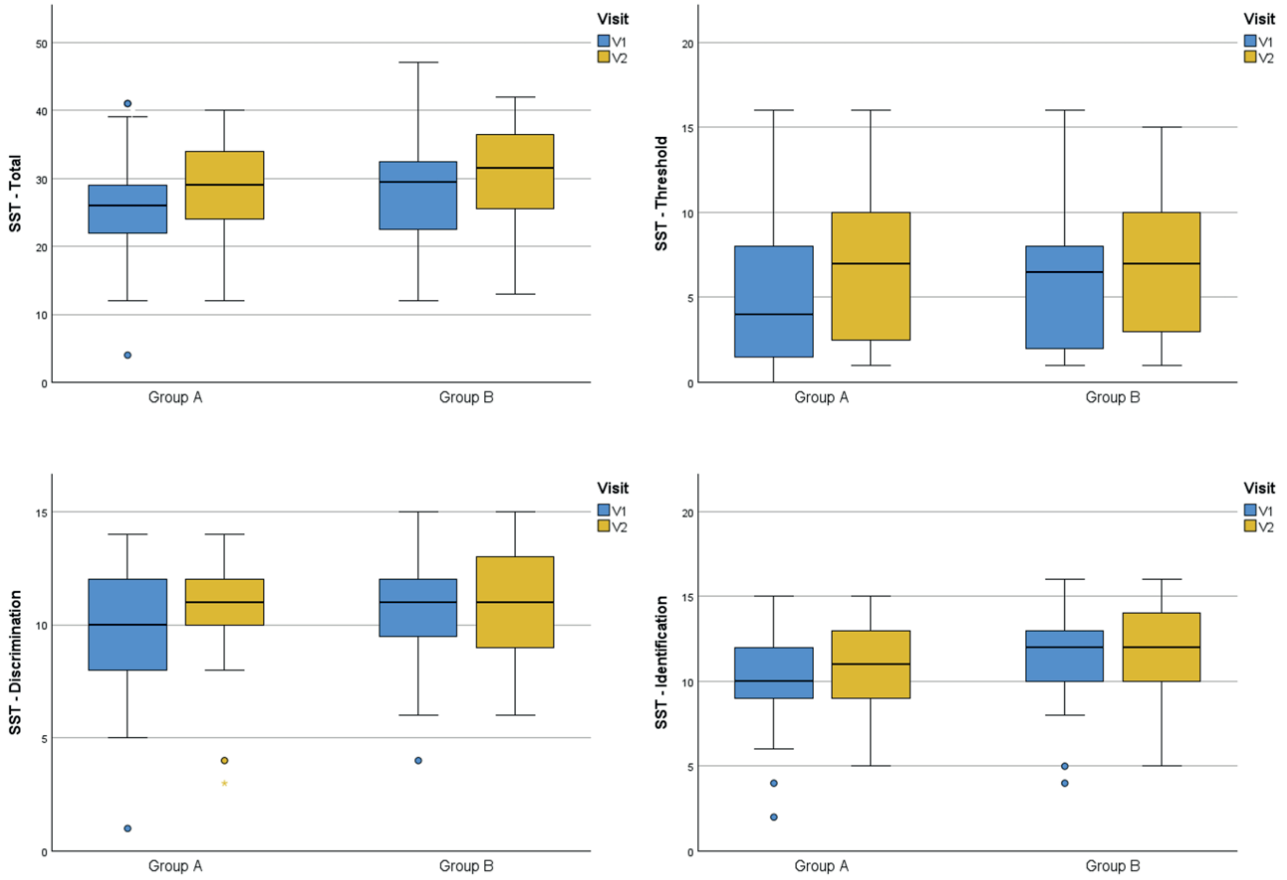

Figure 3. Boxplot of the distribution of SST total and sub-scores for Groups A and B at V1 and V2.

Discussion

This study presents findings on olfactory recovery in PACS patients experiencing prolonged post-COVID-19 olfactory dysfunction using MaMadeleine™. The proportion of normosmic patients exceeded 50%, and there was a significant decrease in qualitative dysfunction (Tables 1 and Table S1 in the supplemental material).

Olfactory recovery - Quantitative aspects

Regarding OPA, overall results (irrespective of group) indicate that T showed better recovery compared to D or I. These findings align with a previous conventional study on PACS OT(9), highlighting differences from non-COVID-19 studies which typically show significant improvements in D and I [26]. Spontaneous recovery studies in PACS [10,27,28] have primarily reported improvements in I and D.

Spontaneous improvement in T typically occurs within the first 4 to 6 months post-COVID-19 infection [27], albeit to a lesser extent than D and I. Beyond 6 months post-infection, T recovery slows down, consistent with subjective and psychophysical findings reported in other studies up to 2 years of follow-up [3,29,30]. The enhanced T-recovery observed with OT may be attributed to neuroepithelium regeneration [31], stimulation effects leading to renewal of olfactory neurons and increased expression of olfactory receptors, as previously indicated in post-OT electro-olfactogram studies [32]. Although this study lacked a control group, these evidence-based explanations from OPA support the OT results and challenge the notion of spontaneous recovery. However, given that the TDI in PACS patients after 18 months of spontaneous recovery is estimated to be around ~30 [33], and our post-OT TDI was 29.1±7.4, we cannot conclusively ascertain the full extent of the OT effect.

OT remains the only validated and recommended [21] treatment for persistent olfactory dysfunction, especially post-viral, as shown in PACS studies [34]. In a controlled non-randomised study, Yaylaci et al. [35] reported significant recovery after 12 weeks of OT, initiated 6 months post-onset. Lechien et al. [6] similarly found benefit from a 15-week OT (starting 3 months post-infection), particularly in Identification, with no further gain thereafter. Pires et al. [36] reported significant UPSIT improvement after one month of olfactory training (4 vs 8 odours), started on average 63.9 ± 24.2 days post-COVID, with no added benefit from using more odours. Our results support OT efficacy even >12 months post-onset. This is encouraging for early pandemic patients (e.g. March 2020) who still seek recovery.

Table 2. Qualitative and quantitative impairment comparison between group A and B from V1 to V2.

Group	Group A (N=43)						Group B (N=40)						
	V1		V2		Δ scores SST		V1		V2		Δ scores SST		p- Δ scores[a]
Quantitative impairments	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SST Scores													
Threshold	5,0	3,7	6,8	4,5	-1,7	5,0	5,8	3,8	6,9	4,3	-1,2	3,5	0,229
Discrimination	9,9	2,9	10,8	2,3	0,9	3,0	10,7	2,4	11,1	2,4	0,4	2,4	0,518
Identification	10,2	2,8	10,9	2,6	0,7	2,0	11,5	2,8	11,8	2,9	0,3	2,4	0,419
TDI	25,1	7,4	28,4	6,9	0,3	0,7	28,0	7,4	29,9	7,8	0,1	0,8	0,195
Qualitative impairments	**N**	**%**	**N**	**%**			**N**	**%**	**N**	**%**			**p[b]**
Olfactory perseverations	3,0	7,1	0,0	0,0			3,0	7,5	0,0	0,0			0,927
Parosmia	24,0	57,1	22,0	51,2			24,0	60,0	23,0	57,5			0,600
Phantosmia	3,0	7,1	3,0	7,0			5,0	12,5	2,0	5,0			0,067
SST classification													0,458
Normosmic	7,0	16,3	18,0	41,8			16,0	40,0	21,0	52,5			
Hyposmic	31,0	72,1	22,0	51,2			22,0	55,0	17,0	42,5			
Anosmic	5,0	11,6	3,0	7,0			2,0	5,0	2,0	5,0			

[SD]=standard deviation. SST = Sniffin' Sticks Test. TDI = SST total score. P-valu ea = Mann-Whitney U test; p-value b = Chi2 test; Δ scores SST = difference of TDI between V1 and V2; p-value Δ scores = significatively of Δ scores between both groups.

Bimodality olfactory training

Bimodal visual-olfactory stimulations aim to enhance central processing of olfactory signals, thereby improving odor perception and identification in patients. Several authors have highlighted bilateral visuo-olfactory stimulation as a method to model both high and low-level cognitive functions [11–13]. Additionally, this type of olfactory stimulation is adaptive in subjective patient perceptions, rather than dichotomous [12]. The more congruent the visual-olfactory pairing, the more pleasant the perception for the patient, facilitating the recall of pleasant memories [37]. Therefore, selecting universally pleasant odors that create a congruent visual-olfactory experience was crucial in developing and selecting odors for MaMadeleine™.
As previously reported in the methodology section, other stimuli types such as colors [38], verbal cues [39], and images [13], could enhance odor discrimination and identification based on published OT protocols. These stimuli were predominantly included in the group B OT protocol. The anatomical region targeted by these co-stimulations is the perirhinal cortex, identified as a processing hub for integrating visual-olfactory information [40].

Unfortunately, we did not observe improved Discrimination (D) or Identification (I) olfactory recovery in the bimodal OT group as anticipated. Randomization resulted in a higher proportion of normosmic patients and better Identification SST scores in group B before OT, potentially biasing the results. However, this outcome may also be attributed to impaired central processing within the visual-olfactory integration hub, resulting from direct brain issues due to persistent inflammation in PACS [41].
Tasks involving D and I are related to specific cognitive domains, notably executive functions and both semantic and episodic memory [42]. Moreover, semantic memory impairment has been reported in 20% of PACS patients and correlates with olfactory loss [43], indicating direct olfactory consequences linked to dysfunction in brain regions connected to the olfactory primary or secondary cortex. Recent studies using positron emission tomography with fluorine-18 labelled fluorodeoxyglucose [44] have highlighted hypometabolism in bilateral orbitofrontal cortex, cingulate gyrus, thalamus, hippocampus, and parahippocampal gyri in PACS patients with persistent olfactory dysfunction complaints lasting ≥3 months. Magnetic resonance imaging has shown morphological and functional changes in these olfactory-connected cortical areas, particularly in grey matter volume of the cingulate gyrus and hippocampus, correlated with persistent olfactory dysfunction in PACS patients [45]. A recent tractography study [46] has identified that these areas are interconnected through the inferior longitudinal fasciculus, which also extends to the visual cortex. The bilateral interactions between the visual and olfactory cortices may have been disrupted by ongoing PACS-related processes, affecting the semantic-internal

temporal hub. This pathophysiological mechanism could have diminished the expected semantic effect in Group B.
A web-application-guided OT protocol was developed for 548 PACS patients using 4 over-the-counter essential oils twice daily, with supporting photos, text, or videos [47]. Over 27.7 days on average, subjective olfactory scores improved from 1.9±1.7 to 4.6±2.8 (Likert scale). Most patients had PACS duration <6 months as only 13% were between 6–12 months. In a randomised controlled study [48], 275 patients received one of four OT types, including uni- or bi-modal protocols with preferred or physician-assigned odours. No inter-group differences were found on UPSIT, but all OT groups improved significantly (+4 points) compared to controls (36% vs 24%). Although non-significant, the patient-preferred bimodal group showed the greatest gain. Interestingly, many selected traditional OT odours (clove, lemon, eucalyptus, rose), reinforcing their established efficacy.

Adherence to the olfactory training

Many authors have highlighted that the duration of olfactory training (OT) is correlated with improved recovery rates, particularly in persistent olfactory dysfunction following COVID-19. Denis et al. [47] reported a 13% higher adherence for training periods exceeding 28 days, with adherence falling from 88% to 56% when OT extended beyond three months [9,21]. In our study, the bi-modal OT program was associated with better adherence; this may in part be due to its more engaging and playful nature, combining visual and olfactory stimuli. However, we cannot exclude the contribution of other factors, such as the simplified once-daily schedule, which may also have improved feasibility. Further studies are needed to disentangle the respective contributions of content and format to adherence.

Olfactory recovery - Qualitative aspects

Qualitative dysfunction significantly improved with MaMadeleine™. While ~30% of patients show persistent quantitative dysosmia 24 months post-COVID-19, qualitative improvement is more variable. Lechner et al. [49] found >80% parosmia prevalence at 1 year. Only one PACS study reported parosmia improvement post-OT [7], while others describe worsening, especially phantosmia [6,9]. In our cohort, parosmia improvement may relate to increased T scores, suggesting peripheral mechanisms such as aberrant olfactory bulb regeneration and altered neuronal proximity in a hypotrophic environment [50]. Given its impact (distress, appetite loss, undernutrition), any symptom improvement is clinically meaningful.

Quality of life

Olfactory-specific quality of life improved after 2 months of MaMadeleine™ OT in both groups. As shown pre-pandemic [21] and in PACS studies [6,7,48], OT improves quality of life, even without full olfactory recovery. Though secondary, this outcome remains crucial given the substantial burden of PACS.

Limits

This study has several limitations. Firstly, randomization introduced bias in the groups before the study, potentially influencing the results, as did the difference in frequency between the bimodal OT protocols (twice a day for group A versus once a day for group B). Moreover, the final sample size of 83 participants is slightly lower than our initial projection of 100. While this reduced the study estimated power from 90% to 85%, the final sample still allows for meaningful inferences regarding OT effects. The study lacks a control group, and the proof of concept regarding MaMadeleine™ efficiency needs validation in larger randomized controlled trials, given our small study population. The study was also limited to a duration of only 2 months (proof of concept), whereas many OT studies typically last 3 months, which could explain the lack of significant differences observed, despite noticeable trends.

Conclusion

This study serves as a proof of concept for MaMadeleine™ efficiency. By employing this innovative olfactory bi-modal training kit, we advocate for both quantitative and qualitative olfactory recovery, as well as improvements in olfactory-specific quality of life in post-acute COVID-19 syndrome. Bimodal training may enhance adherence to the regimen. Further studies are necessary to refine the target population and optimal duration for using MaMadeleine™.

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Authors' contributions

CV, MP, VM, AD, XF, AP and AG conceptualized the study, MP and AG create the olfactory training pipeline and the application build, CB formulated odours kit, SB designed the olfactory training kit, AD computed the web-application and the connections platform, MP, CB, XF and AG choose the odours, CV and MP acquired the data, VM provided all the statistics, CV write the first manuscript draft, all authors review the first draft.

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Conflicts of interest

There is no conflict of interest.

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SUPPLEMENTARY MATERIAL

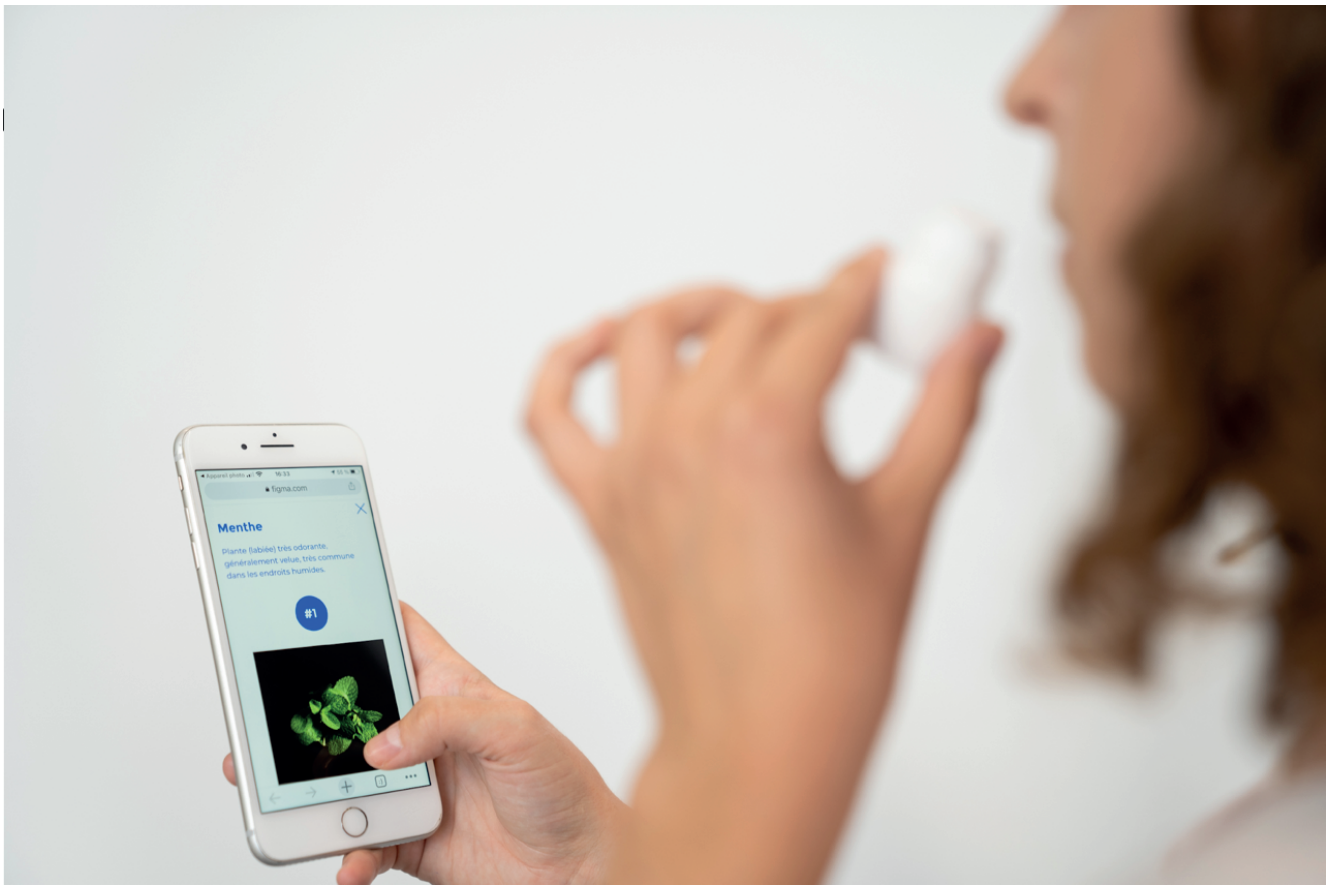

Figure S1. Illustration of Group A olfactory training session with Mint. The Sorbarod number (#1) and a picture of the fragrance is displayed.

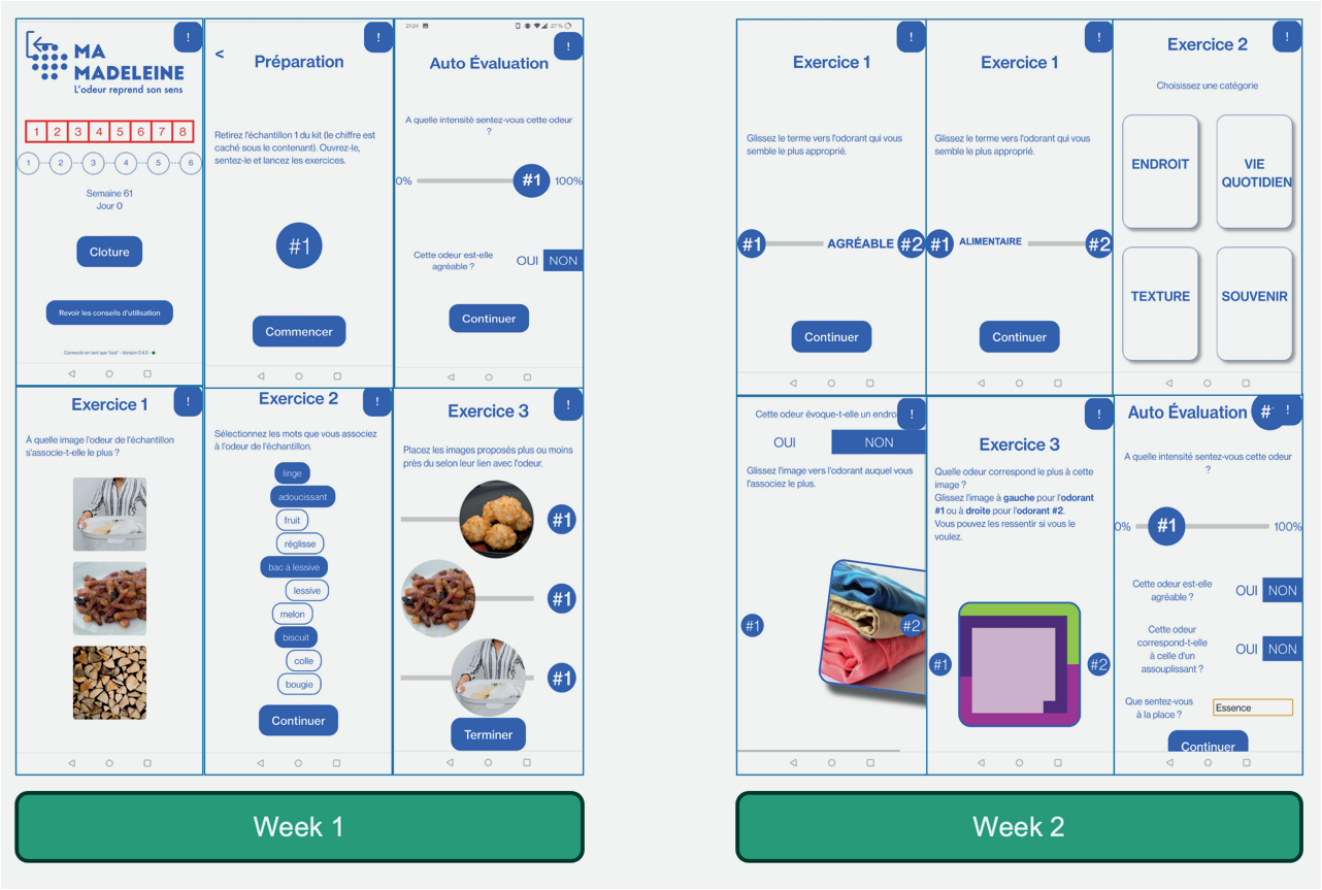

Figure S2. Illustration of Group B olfactory training sessions with screenshots of application functioning the week 1 and 2 of each 2 weeks loop. These exercises are only examples of what was done every day. In week 1 (non-labelled sorbarods) we can see a progression screen, a self-subjective visual analogic scale of quantitative perception, some visual semantic picture association tasks and a word semantic association task and. In week 2 (labelled and picture-illustrated smells in the three sorbarods) we can see hedonic tasks, episodic memory tasks, more visual semantic picture association task and colour recognition tasks. In each week loops, tasks were randomly displayed to the patient to keep a high level of entertaining using the app.

Table S1. Qualitative and quantitative impairment comparison between V1 and V2 in overall population.

Group	V1 (N=83)		V2 (N=83)		
Quantitative impairments	**Mean**	**SD**	**Mean**	**SD**	**p-value**
SST Scores					
Threshold	5,4	3,8	6,8	4,4	**0,001**
Discrimination	10,3	2,7	10,9	2,3	**0,044**
Identification	10,8	2,8	11,3	2,8	**0,026**
TDI	26,5	7,5	29,1	7,4	**<0,001**
Qualitative impairments	**N**	**%**	**N**	**%**	**p[b]**
Olfactory perseverations	7	8,4	6	7,6	1,000
Parosmia	68	81,9	48	61,5	**<0,001**
Phantosmia	27	32,5	8	10,1	**<0,001**
SST classification					**0,003**
Normosmic	23	27,7	39	47,0	
Hyposmic	53	63,9	39	47,0	
Anosmic	7	8,4	5	6,0	

SD = standard deviation. SST = Sniffin' Sticks Test. TDI = SST total score.