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Original Article

Losing olfaction in COVID-19: Screening, training and effects on quality of life

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SUMMARY

Background & aims: Olfactory disorders impact mental health, with adverse effects on quality of life, particularly in the area of eating. Despite their high prevalence in the population, olfactory disorders are poorly managed, with patients still lacking easy access to rapid diagnosis and treatment. In this context, the present study offers a new screening tool and compares the efficiency of different olfactory training protocols.

Methods: A screening test was set up and different olfactory training paradigms were compared for their effect on the recovery of the sense of smell on the one hand, and quality of life on the other. The study population was composed of post-COVID-19 dysosmic patients (with a loss of more than 6 weeks). Three training protocols were used, differing in terms of number of odors and in format (either lab-supplied odorant kits, or the use of odorants found at home). All three protocols were implemented over a 12-week period.

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Results: The screening test distinguished dysosmics from normosmics with an accuracy of 73%. During training, 69% of patients completed the evaluation protocol and 77% of them performed more than half of the training sessions, resulting in a 53% completion rate. Olfactory performances improved significantly after training, irrespective of the training paradigm and 59% of patients displayed a clinically significant improvement of their sense of smell. These improvements were positively associated with assiduity along training. Finally, olfactory disorders negatively affected quality of life. After olfactory training, this overall negative impact on quality of life was reduced, especially with regard to the pleasure of eating.

Conclusion: This study introduces a new screening tool for olfactory deficits. It also provides important insights into the optimization of olfactory training protocols and their effects on quality of life, and on eating behavior in particular.

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Introduction

Smells fulfill important signaling and hedonistic functions in daily life. Therefore, olfactory loss significantly impacts physical and mental health, through increased domestic accidents [1], social and sexual insecurity [2] and significant changes in eating habits [3]. As food odors play a predominant role in the tasting experience [4], some coping mechanisms (e.g. increased use of salt or sugar) used to enhance flavor and regain pleasure might become ingrained, leading to nutritional problems [5]. This overall impact on life quality is reflected in the high prevalence of depressive symptoms in patients with olfactory disorders (i.e. dysosmic patients) [5].

Olfactory disorders affect 15–20% of the population in Europe and the USA [6–9] and range from quantitative deficits (hyposmia, anosmia) to qualitative modifications (parosmia, phantosmia) [10]. Viral infection is one of the most predominant etiologies [11,12], as with SARS-COV2 responsible for COVID-19, whose first variants induced olfactory disorders in more than half of the infected patients [13,14]. Of these, nearly 25–30% developed persistent olfactory deficits (i.e. lasting longer than 6 months), indicating that spontaneous recovery is not systematic [15,16].

Despite their high prevalence, olfactory disorders are insufficiently managed, in terms of diagnosis, prognosis and therapy. For **diagnosis**, olfactory self-assessment is unreliable [7,17] and psychophysical diagnostic tools are too rarely implemented in daily clinical care [18], due to practical issues. Furthermore, these tests are barely usable as **screening** tools in a health crisis context since they are not designed for single use or self-administration. **Olfactory training** is a promising therapeutic option [19,20], because trained patients have higher olfactory recovery compared to controls [20,21], but this intervention is infrequently available in routine care. Moreover, its efficacy remains highly variable [22], highlighting the need to consider variables, such as age, baseline olfactory performances, deficit duration or etiology. While some parameters of training protocols have been studied (duration, intensity, odor renewal etc.) [21,23–26], the variability of the results also reveals the necessity to improve treatment adherence and monitoring.

The global aim of this study was to optimize the management of olfactory disorders by improving screening of olfactory deficits and remediation strategies based on olfactory training. In **Study 1**, we developed and tested a new scratch-and-sniff screening tool suitable for clinical use and self-administration. In **Study 2**, we tested three olfactory training regimens. Two regimens based on laboratory-provided kits allowed us to test whether a higher number of odors smelled daily would enhance training efficacy. A third training protocol based on household products, designed to improve patients' accessibility, was also tested. To standardize self-administration, boost overall

treatment adherence and monitor patients' assiduity, the daily training sessions were performed on a dedicated web platform. Benefits on olfactory perception and quality of life (especially eating) were investigated.

Material and method

Ethics statement

Informed written consent was obtained from all participants. This study was performed in accordance with the Declaration of Helsinki on Biomedical Studies involving human subjects. The study design and participants' consent were approved by the Sud-Méditerranée III ethical review board.

Participants

Participants were recruited for two studies in parallel: **Study 1**, consisting of a single evaluation visit in which a screening test was administered, and **Study 2** which consisted of 3 evaluation visits along an olfactory training at home. The single visit of study 1 was included in one of the three visits of study 2.

A total of 102 patients were recruited from spring 2020 to summer 2022 in 4 different hospitals (Hôpital Nord-Ouest, Hôpital Édouard-Herriot, Infirmerie protestante de Lyon, Centre Hospitalier Lyon Sud). Patients were adults previously diagnosed with COVID-19 and suffering from persistent olfactory disorders for more than 6 weeks (screened using the ETOC-16 test [27]). Among all patients, 3 were found to be normosmic and 3 had an incomplete initial olfactory test, leaving a total of 96 patients included in data analysis. Patients had no neurological or psychiatric history, no pre-existing olfactory disorders at the time of COVID-19 infection and no conduction-dysosmia based on nasofibrosopic examination.

All 96 patients took part in Study 2 (Table 1). For Study 1, data was missing for 11 patients, leading us to include 85 patients (out of 96); an additional 23 control participants were recruited as normosmics. Olfactory status (see section 2.3.1) of Study 1 participants, that we took into account to place them in the normosmic control or dysosmic group, was the one recorded at the time of the visit (that is, first visit of Study 2 most of the time, and third visit of Study 2 for some patients). As it turned out that some participants did actually not belong to their a priori group (4 patients and 2 controls), overall Study 1 was conducted on 83 dysosmic participants (81 post-COVID-19 patients and 2 dysosmics of unknown etiologies) and 25 normosmic participants (21 recruited as such and 4 normosmics post-training) (Table 1).

Table 1
Characteristics of the included participants for each study

	Study 1		Study 2
	Controls	Dysosmics	Dysosmic patients
N	25	83	96
Age	37.4 ± 13	38.8 ± 13.6	39.4 ± 13.5
Smoker	1	9	12
Ratio ♂/♀	0.14	0.41	0.3
ETOC score (%)	90.6 ± 5.6	54.7 ± 18.8	51.4 ± 18.9
Hyposmic		63	72
Anosmic		20	24
Disorder duration (day)		185 ± 107	183.2 ± 102
^a Parosmia		44	55
^a Phantosmia		36	38
^a Permanent olfactory disorder		71	84
^a Stuffy nose		12	13
^a Taste disorder		60	75
^a Trigeminal disorder		13	16

^a self-declared.

Study 1: screening

Evaluation of the olfactory performances

At first, participants were evaluated using the ETOC-16 test which consists of 16 rows of 4 vials, all filled with odorless mineral oil as a solvent. In each row, only one vial contained an odorant diluted in the solvent. Odorants were different between the rows (total of 16 odorants). Patients had to smell the 4 vials of one row successively. To assess olfactory detection/localization performances, participants had to localize the odorized vial within each row. A localization score (range 0–16) was calculated by summing the properly localized odors. Then, to assess identification performances, patients had to sniff again the vial they selected and identify the perceived odor by choosing between 4 proposed items. An identification score (range 0–16) was calculated by summing the properly identified odors. Using normative data from a previous study [27], both localization and identification scores were used to classify patients into two distinct groups: normosmic or dysosmic (hyposmic and anosmic).

Then, participants were evaluated using the screening test which consists of 5 foldable and numbered cards based on the “scratch and sniff” concept [7]. Microcapsule-based ink was printed on cards. The first card was the control blank with no odor. Odorants (quality, CID or Compound ID number, concentration in ink in % v/v) used on the 4 odorized cards were: trans-anethol (anis, 637563, 22.5%), L-carvone (mint, 439570, 22.5%), iso-amyl acetate (banana, 31276, 5.6%) and alpha-pinene (pine, 6654, 22.5%). To release the odorant, participants had to scratch the colored circle using a wooden stick. Then, they had to bring the colored circle of the card close to the nose in order to sniff the odor. Participants had to rate the perceived intensity (very low; low; medium; strong; very strong) for each card. Then, they had to identify the odor among four proposed items (blank card: apricot, caramel, butter, bread; anis card: anis, cinnamon, fish, tea; mint card: nut, olive, onion, mint; banana card: almond, lemon, carrot, banana; pine card: tar, pine, orange, cucumber).

Data analysis

All statistics were performed using R software [28]. Data normality and homoscedasticity were assessed by Shapiro-Wilk and Bartlett tests. Alpha value was set to 0.05 for all statistical tests.

To examine whether the scale of perceived intensity in the scratch and sniff test was used differently by normosmics and dysosmics, we compared the perceived intensity rating (very low=1; low=2; medium=3; strong=4; very strong=5) of each card between normosmics and dysosmics. As normality condition was not met, Wilcoxon tests with Bonferroni correction were used.

To analyze the scratch and sniff screening test performances, a perceived intensity score was computed from the mean response scale and an identification score was set as the number of correct identification responses for the 4 scented cards. Note that only the 4 odorant cards were used for this scoring. To test if the screening test's scores could distinguish between olfactory statuses (normosmic, dysosmic) defined by the ETOC-16 score, a Wilcoxon test was performed to test the effect of olfactory status on the 2 scores of the screening test (perceived intensity and identification).

Last, to test if the identification and intensity scores of the screening test could accurately predict olfactory status (dysosmic or normosmic), a classification model was built using the package ‘Caret’ [29]. A leave one out cross-validation method was run on a linear discriminant model. As olfactory statuses were represented in an unbalanced way in our population (77% dysosmics vs 23% normosmics), a down sampling method was used to reduce the number of dysosmics from the data used to train the model. The same analysis was then run on anosmics and normosmics to evaluate the performance of the test for olfactory loss screening. In this case, no resampling method was used as olfactory statuses were already balanced (56% anosmics vs 44% normosmics).

Study 2: training

Training regimens

Patients were pseudo-randomly assigned to 3 different olfactory training regimens: LabKit-1, LabKit-3 or HomeKit. All olfactory training regimens lasted 12 weeks and were done at home in autonomy.

LabKit-1 and LabKit-3 differed in the number of odorants smelled daily (1 vs 3 odorants per day). The order of presentation of odorants was pseudorandomized to maximize the time between each exposure to the same odorant. Patients were given an olfactory training kit which consisted of a case containing 7 triplets of vials for a total of 21 vials. They were also given an individual access code to a web platform guiding the daily training session. Patients were instructed to perform the training session each day at the same hour and preferentially away from mealtime. During each session, patients had to log into the web platform (LimeSurvey) and smell a triplet of vials: one contained one of the 7 odorants, the 2 others contained only the solvent (odorless mineral oil). Patients had to choose which vial contained the odorant (localization task) and to rate the perceived intensity of the odor of the selected vial (intensity rating task). For LabKit-3, these steps were repeated for each of the 3 different triplets. These daily tasks allowed a goal-oriented exposition, favoring the patient's engagement in their training.

For HomeKit, patients were not given any training kit but had to choose 5 odorous household products they had at home. Training on the platform was similar to LabKit-1 and LabKit-3, except those patients could not perform a localization task and thus only rated the intensity of the 5 selected odorous household products. This form of training with reduced material constraints was designed to improve accessibility of olfactory training (which was crucial at the time the study was conducted, i.e. during the sanitary crisis when the demand for care was high).

For all training regimens, to prevent loss of motivation and boost overall treatment adherence, we set up a frequent follow-up using progression graphs generated by the web platform on which patients performed their daily training sessions. This web platform was also useful to both standardize self-administration of olfactory training and to monitor patients' assiduity. A bi-monthly meeting by phone call was also organized between patients and clinical teams to favor treatment adherence. Instructions were adjusted if needed and patients had the possibility to visualize their progression on graphs based on their daily detection and intensity rating tasks.

Odorants

In LabKit-1 and LabKit-3, seven odorants were used, as detailed in Table 2. These odorants were selected to cover as much as possible the olfactory perceptual space and included the 4 odorants used in the initial training protocol proposed by Hummel [20]. For HomeKit, patients had to choose 5 odorous household products they had at home (e.g. jam, coffee, toothpaste ...) following guidelines of the instruction sheet provided. In particular, odorous household products had to be varied, well distinct, stable in time and intense (see Annex 1).

Assessment of olfactory performances along training

Alongside olfactory training, patients had 3 visits with the ENT practitioners: initial (inclusion) visit, at 6 weeks (mid-term) and at 12 weeks (end of olfactory training). During these visits, chemosensory impairments were subjectively assessed with a questionnaire and psychophysically with the standardized ETOC-16 test [30] (see description above in section 2.3.2). The overall score to the ETOC-16 test was the percentage of correct localization/detection and identification. To allow comparison with studies that used the Sniffin'Sticks, the minimum score improvement considered as clinically relevant was set at 12%, corresponding to 5.5/48 Threshold-Discrimination-Identification points improvement in the Sniffin'Sticks test. This threshold was defined as the minimal score increase corresponding to a significant improvement from the majority of patients' point of view [31].

Table 2

List of odorants used in LabKit-1 and LabKit-3

Molecule	LabKit-1 & LabKit-3						
	2-phenyl ethanol	Cineol	Citronellal	Eugenol	cis-3hexenol	Terpinene-4-ol	d-limonene
Quality	rose	eucalyptus	lemongrass	cloves	grass	damp	citrus
CID number	6054	2758	7794	3314	5281167	11230	440917
Category	flowery	resinous	fruity	aromatic	herbaceous	foul	fruity
Concentration in % v/v	8	16	1	8	1	5	4

Assessment of quality of life before and after training

To evaluate the benefits of the different training regimens on living conditions, quality of life was assessed before (initial visit) and after olfactory training (12 weeks) using a quality of life olfaction-related questionnaire, as previously described [32]. As “quality of life” is an umbrella concept with many aspects [33], we aimed to evaluate living conditions in domains where olfaction plays a predominant role, especially in health, emotional and social well-being [5]. For that purpose, we used a quality of life-olfaction related questionnaire aiming to cover predominant roles of olfaction in these areas: hedonic pleasure (“Do you enjoy eating?”, “Do you enjoy smelling flowers?”), food behavior (“Do you add salt to your meal?”, “Do you add sugar to your meal?”, “Do you add condiments (spices, hot peppers) to your meals?”, “Do you add condiments (mayonnaise, oil) to your meals?”), interpersonal relationship (“Do you prefer to eat alone?”, “Do you seek out the scent of your relatives?”), hygiene (“Do you seek to control your own body odor”, “Do you wear perfume?”, “Do you take showers?”) and danger detection (“Do you let meals burn?”, “Do you let clothes burn?”, “Do you have domestic accidents?”, “Do you perceive gas and smoke”, “Do you eat spoiled food?”). The response scale was adapted to the brutal onset of olfactory disorders in the COVID-19 etiology as follows: “more than before”; “less than before”; “as usual”.

Data analysis

All statistics were performed using R software [28]. Data normality and homoscedasticity were assessed by Shapiro-Wilk and Bartlett tests. Alpha value was set to 0.05 for all statistical tests. Compliance with olfactory training was defined as the % of patients who made it to the last visit and assiduity as the number of training sessions completed (out of 84 possible sessions). The 3 olfactory training regimens (LabKit-1, LabKit-3, HomeKit) were compared in terms of patient's characteristics and scores. For age, disorder duration, ETOC-16 score and assiduity among groups, a one-way ANOVA was used when the normality condition was respected, otherwise a Kruskal test was performed. A Fisher test was used to compare proportions of initial olfactory statuses (hyposmic and anosmic) and genders (male and female) among groups.

The response scale of the quality-of-life questionnaire was converted to a numeric one: “more than before”, “less than before”, “as usual” were respectively set as 1, -1 and 0. An impact score of olfactory disorders on quality of life was computed by summing all responses that were different from 0 (“as usual”). To test the progression of olfactory performances and quality of life with time as well as the effect of olfactory training regimen, a linear model was built with repeated measures for time (before, mid-term and after training). Training assiduity was set as cofactor. As age and disorder duration are known to influence olfactory training efficiency [23,24], they were also set as cofactors. The model was thus: *dependent variable* ~ *time* * *olfactory training regimen* + *age* + *disorder duration* + *assiduity* + (1 | *patient*). A variance analysis (ANOVA) was then run on the model to test the effect of time and olfactory training regimen on the following dependent variables: ETOC-16 score and impact score of olfactory disorders on quality of life. As data normality was not met for the ETOC-16 score, it was scaled for this analysis. To correlate progression of olfactory performances with patient's characteristics, progression in ETOC-16 score was defined as the difference in ETOC-16 score in % between before and after training. After each ANOVA and Kruskal test, post-hoc tests were performed using Student t-tests or Wilcoxon tests in the event of non-normality. Post hoc tests were corrected using Bonferroni correction.

Results

Study 1: screening

When looking at perceived intensity ratings of the screening test, dysosmics and normosmics (classified as such according to their ETOC-16 score) significantly differed for each of the 4 odors (Anis card: $W=475, P<0.001$; Mint card: $W=548, P<0.05$; Banana card: $W=585, P=0.02$; Pine card, $W=605, P<0.05$), but not for the blank ($W=972, P=0.27$) (Figure 1A). Thus, the differences in intensity indeed

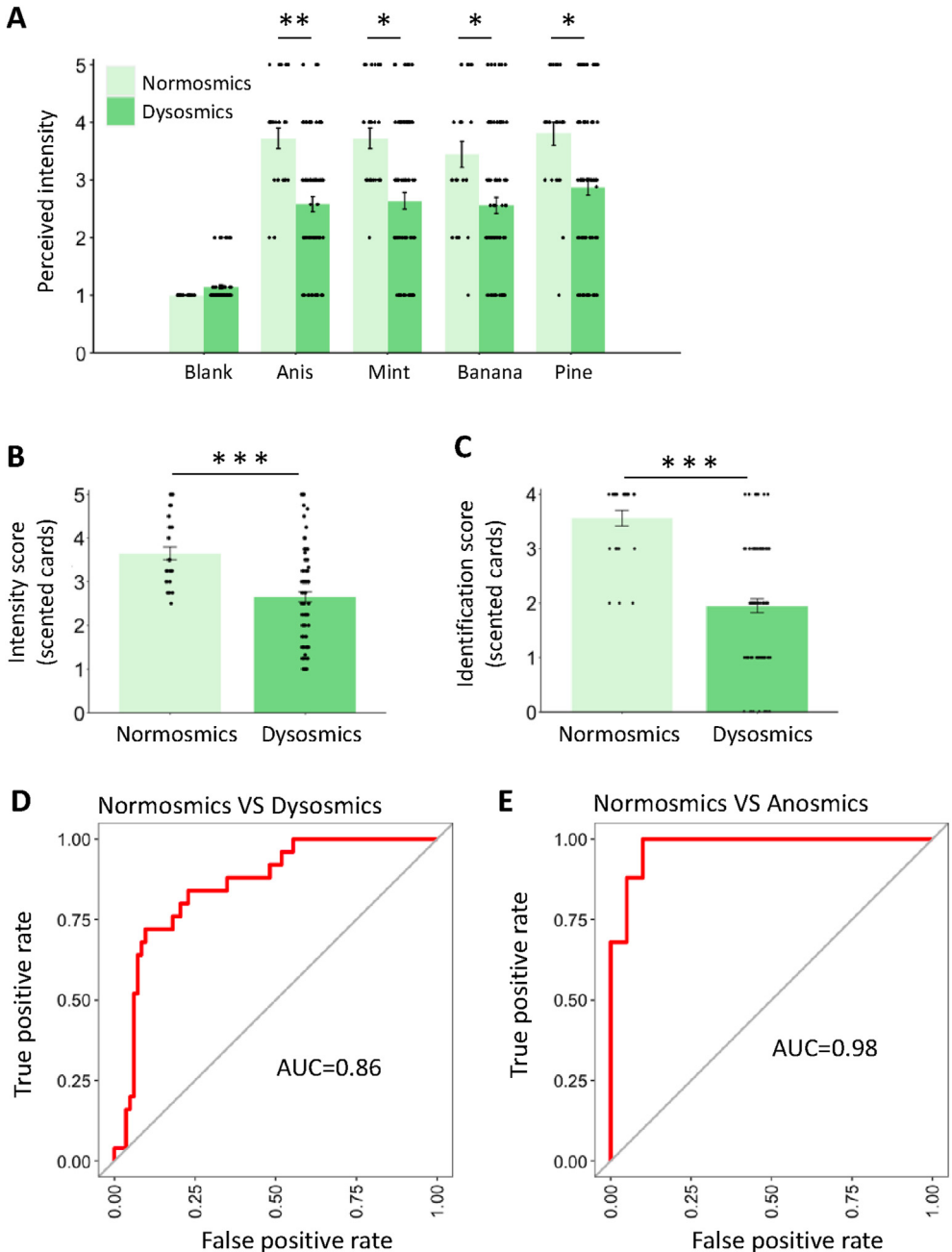


Figure 1. Prediction of the olfactory status by the olfactory screening test.

A) Perceived intensity ratings among the 5 cards of the screening test for both normosmics and dysosmics determined by the ETOC-16 score (Wilcoxon test with Bonferroni correction). B) Mean perceived intensity scores of the 4 scented cards of the screening test for both normosmics and dysosmics (Wilcoxon test). C) Mean identification scores of the 4 scented cards of the screening test for both normosmics and dysosmics (Wilcoxon test). Data are expressed as mean±SEM. Dots represent individual patients and participants. Normosmics: n=25, Dysosmics: n=83. * $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$. D) Mean ROC curve of the 108 acquired models representing the true positive rate (sensitivity) for the false positive rate (specificity) with normosmics vs dysosmics. E) Mean ROC curve of the 108 acquired models representing the true positive rate (sensitivity) for the false positive rate (specificity) with normosmics vs anosmics.

Table 3
Confusion matrix of the model predicting normosmics vs dysosmics

		ETOC-16 classification	
		Normosmics	Dysosmics
Model prediction	Normosmics	21	25
	Dysosmics	4	58

reflect differences in perceived intensity rather than in the use of the measurement scale by the two groups. Odor intensity ratings can therefore be considered as a reliable variable.

When considering the mean scores over the 4 scented cards, dysosmics rated intensity lower than normosmics (dysosmics: 2.7 ± 1.1 , normosmics: 3.7 ± 0.8 , Wilcoxon test $W=1579$, $P < 0.0001$) (Figure 1B). In the same way, dysosmics had lower identification scores than normosmics (dysosmics: 2 ± 1.2 , normosmics: 3.6 ± 0.7 , Wilcoxon test $W=1801.5$, $P < 0.0001$) (Figure 1C).

In addition, the 4-card screening test mean intensity score was positively correlated with the ETOC-16 localization score ($r=0.51$, Spearman, $P < 0.0001$) (Supp. Figure 1A). The screening test and the ETOC-16 identification scores were also positively correlated ($r=0.72$, Spearman, $P < 0.0001$) (Supp. Figure 1B).

To test whether the perceived intensity and identification scores of the screening test could predict the olfactory status of participants (**normosmic or dysosmic**), a leave-one-out cross validation was run using a random forest training model. Area Under the Curve of the mean Receiver Operating Characteristic (ROC) curve was 0.86 (Figure 1D). Misclassification was due to 25 dysosmics (out of 83) classified as normosmics (false negative) and 4 normosmics (out of 25) classified as dysosmics (false positive) (Table 3), for a total correct classification rate of 86%, a sensitivity of 70% and a specificity of 84%. Probability of displaying dysosmia according to score combinations of the screening test are shown in Supp. Figure 2, along with the detailed probabilities (Supp. Table 1). To go further, we also tested if scores of the screening test could predict whether participants were **normosmic or anosmic** using the same method. Area Under the Curve of the mean Receiver Operating Characteristic (ROC) curve was 0.98 (Figure 1E). Misclassification was due to 1 anosmic (out of 20) classified as normosmic (false negative) and 3 normosmics (out of 25) classified as anosmics (false positive) (Table 4), for a total correct classification rate of 91%, a sensitivity of 95% and a specificity of 88%. Therefore, the screening test seems to be able to distinguish dysosmics from normosmics and to accurately predict olfactory status in 73% of cases (79/108), up to 91% (41/45) when predicting for anosmics vs normosmics only.

Study 2: training

Compliance and assiduity in olfactory training

The training experiment started with a cohort of 96 patients, among which 30 patients did not make it to the last evaluation visit (after training), leading to a mean percentage of compliance of 69%. This compliance was not significantly different among olfactory training regimens (67% in LabKit-1, 78% in LabKit-3 and 58% in HomeKit; $X^2_{(2)} = 0.58$, $P=0.75$).

These 30 patients were then discarded from the analysis and assiduity (i.e. the number of training sessions that were performed out of 84 scheduled) was measured for the 66 remaining participants who completed the three evaluation visits (before, mid-term and after training). Assiduity significantly differed according to olfactory training regimen (Kruskal test, $H_{(2)}=6.78$, $P=0.03$). Compared to LabKit-3, HomeKit assiduity was significantly lower (post-hoc Wilcoxon test with Bonferroni correction, LabKit-1 vs LabKit-3: $W=265$, $P=0.91$; LabKit-1 vs HomeKit: $W=222$, $P=0.24$; LabKit-3 vs HomeKit:

Table 4
Confusion matrix of the model predicting normosmics vs anosmics

		ETOC-16 classification	
		Normosmics	Dysosmics
Model prediction	Normosmics	22	1
	Dysosmics	3	19

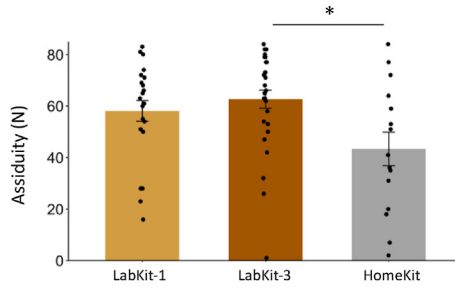


Figure 2. Patients in the HomeKit training protocol displayed lower assiduity.

Assiduity in number of sessions performed (out of 84) for LabKit-1, LabKit-3 and HomeKit training protocols (before the assiduity filter). Data are expressed as mean±SEM. Dots represent individual participants. n=22 for LabKit-1, n=29 for LabKit-3 and n=15 for HomeKit. Kruskal test followed by post-hoc Wilcoxon test with Bonferroni correction * $P < 0.05$.

$W = 319, P = 0.04$) (Figure 2). When looking in more detail, 15 patients (4 of LabKit-1, 3 of LabKit-3 and 8 of HomeKit) completed less than half of the training sessions and were thus excluded from further analysis, leading to a total of 51 patients.

Efficacy of the different olfactory training regimens on olfactory perception

On the 51 patients selected as explained above, we compared the efficacy of the three olfactory training regimens. We first analyzed several characteristics of the patients within the groups (Table 5). Age did not differ significantly between groups (One way ANOVA, $F_{(2,48)} = 2.48, P = 0.09$), nor did the gender distribution (Gender: Fisher test, $P = 0.29$), the disorder duration (Kruskal test, $H_{(2)} = 0.21, P = 0.9$), the initial ETOC-16 score (Kruskal test, $H_{(2)} = 2.98, P = 0.23$) or the initial olfactory status proportions (Fisher test, $P = 0.21$). Assiduity was also similar between the groups (One way ANOVA, $F_{(2,48)} = 0.18, P = 0.84$).

To test the efficacy of the different olfactory training regimens, we examined the evolution of olfactory performances during olfactory training. We observed a significant effect of time on the ETOC-16 score (ANOVA, $F_{(2,77)} = 13, P < 0.0001$), indicating that ETOC-16 score improved during training, but no effect of olfactory training regimen ($F_{(2,77)} = 1, P = 0.37$) and no significant time-by-olfactory training regimen interaction ($F_{(4,77)} = 0.5, P = 0.74$) (Figure 3A). Overall, the ETOC-16 score increased during training regardless of olfactory training regimen. None of the cofactors appeared significant (age: $F_{(1,77)} = 0.38, P = 0.54$; disorder duration: $F_{(1,77)} = 1.29, P = 0.26$; assiduity: $F_{(1,77)} = 0.003, P = 0.96$). Among the 51 patients, 30 displayed a clinically significant improvement (i.e. > 12% increase in ETOC-16 score), reaching an average recovery rate of 59%. 17 did not progress significantly (progression between 0 and 12%) and 4 saw their score worsened (progression < 0). Those with negative progression were significantly older than those with clinically significant progression (One way ANOVA, $F_{(2,48)} = 3.88, P = 0.03$; negative progression: 58 ± 12 years; no progression: 41 ± 12 years; positive progression: 39 ± 13 years) according to post-hoc t-test with Bonferroni correction (negative vs positive progression:

Table 5
Patients' characteristics and scores for each training regimen

	LabKit1	LabKit3	HomeKit	
N	18	26	7	
Age	36.06 ± 13.61	44.42 ± 12.84	44 ± 8.74	$P = 0.09$
Women	14	18	7	$P = 0.29$
Men	4	8	0	
Hyposmic	14	20	3	$P = 0.21$
Anosmic	4	6	4	
Disorder duration (day)	200.5 ± 135.51	164.37 ± 83.13	149 ± 80.56	$P = 0.9$
ETOC score (%)	57.81 ± 16.2	52.52 ± 21.2	41.07 ± 20.84	$P = 0.23$
Assiduity (Nb of training sessions)	65.78 ± 9.97	67.62 ± 11.60	65.71 ± 12.43	$P = 0.84$

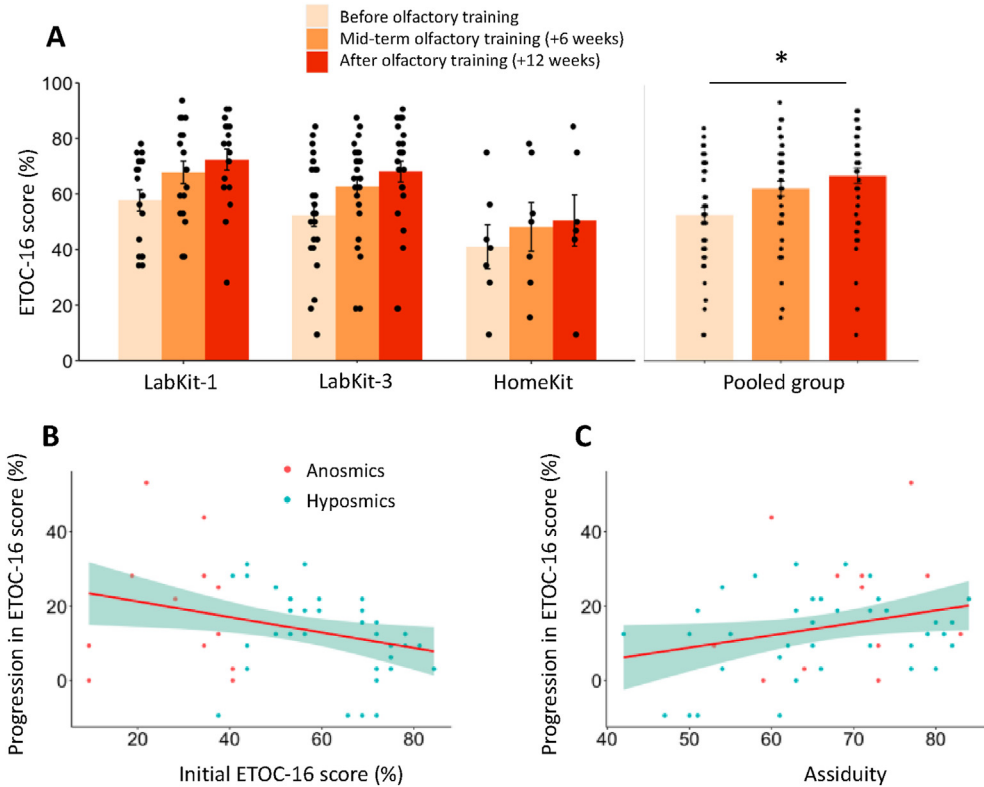


Figure 3. Improvement of ETOC-16 score along training is independent of training regimen.

A) ETOC-16 score in percentage before, at mid-term (6 weeks) and at the end of olfactory training (12 weeks) for LabKit-1, LabKit-3 and HomeKit olfactory training protocols and pooled group. ANOVA followed by post-hoc Wilcoxon test with Bonferroni correction, * $P < 0.05$. Data are expressed as mean \pm SEM. Dots represent individual participants. $n = 18$ for LabKit-1, $n = 26$ for LabKit-3, $n = 7$ for home-Kit, $n = 51$ for pooled group. B) Negative correlation between the progression in ETOC-16 score in % and the initial ETOC-16 score in % ($r = -0.34$, Spearman). C) Positive correlation between the progression in ETOC-16 score in % and the assiduity ($r_{(49)} = 0.28$, Pearson). A linear smooth line is represented in red. Points represent individuals, anosmics in red and hyposmics in blue, $n = 51$.

$T = -2.84$, $P = 0.02$; negative vs neutral progression: $T = -2.52$, $P = 0.06$; positive vs neutral progression: $T = 0.45$, $P = 1$). However, the progression of ETOC-16 score was not significantly correlated with age ($r_{(49)} = -0.23$, Pearson, $P = 0.11$). Disorder duration was not correlated with progression either ($r = -0.18$, Spearman, $P = 0.26$). Interestingly, progression in ETOC-16 score was negatively correlated with the initial ETOC-16 score ($r = -0.34$, Spearman, $P = 0.02$) (Figure 3B) and positively correlated with assiduity ($r_{(49)} = 0.28$, Pearson, $P = 0.04$) (Figure 3C). In conclusion, olfactory training with the two LabKits and the HomeKit improved the ETOC-16 score of post-COVID19-patients and was more efficient in patients with low initial ETOC-16 score and in patients displaying higher assiduity toward training.

Efficacy of the different olfactory training regimens on quality of life

When questioned before starting olfactory training, post-COVID-19 patients responded significantly differently from “as usual” for the items “eating pleasure” (Wilcoxon test with Bonferroni correction, $V = 18.5$, $P < 0.0001$), “pleasure in flower” ($V = 78$, $P < 0.0001$), “let food burn” ($V = 464$, $P < 0.0001$), “perceive smoke and gas” ($V = 36$, $P < 0.0001$), “seek to control own body odor” ($V = 336$, $P < 0.001$), “add salt to food” ($V = 311$, $P < 0.001$) and “add spices to food” ($V = 230$, $P < 0.05$) of the questionnaire (Figure 4A). After olfactory training, only the “eating pleasure” item was found to be significantly

improved compared with before training (Wilcoxon test with Bonferroni correction, $V=6.5$, $P=0.048$) (Figure 4A).

We also examined the evolution of the overall quality of life along training and observed a significant effect of time on the impact score of olfactory disorders on reported quality of life ($F_{(1,4)}=4.54$, $P=0.04$) but no effect of olfactory training regimen ($F_{(2,4)}=0.23$, $P=0.8$) and no time-by-olfactory training regimen interaction ($F_{(2,4)}=1.36$, $P=0.27$). None of the cofactors were significant (age: $F_{(1,4)}=0.5$, $P=0.48$; disorder duration: $F_{(1,4)}=0.002$, $P=0.97$; assiduity: $F_{(1,4)}=0.43$, $P=0.52$) (Figure 4B). Thus, olfactory disorders negatively impact the quality of life of post-COVID-19 patients suffering from persistent olfactory disorders, in predominant areas of olfaction. After olfactory training, this overall negative impact on the quality of life is reduced, especially in terms of eating pleasure.

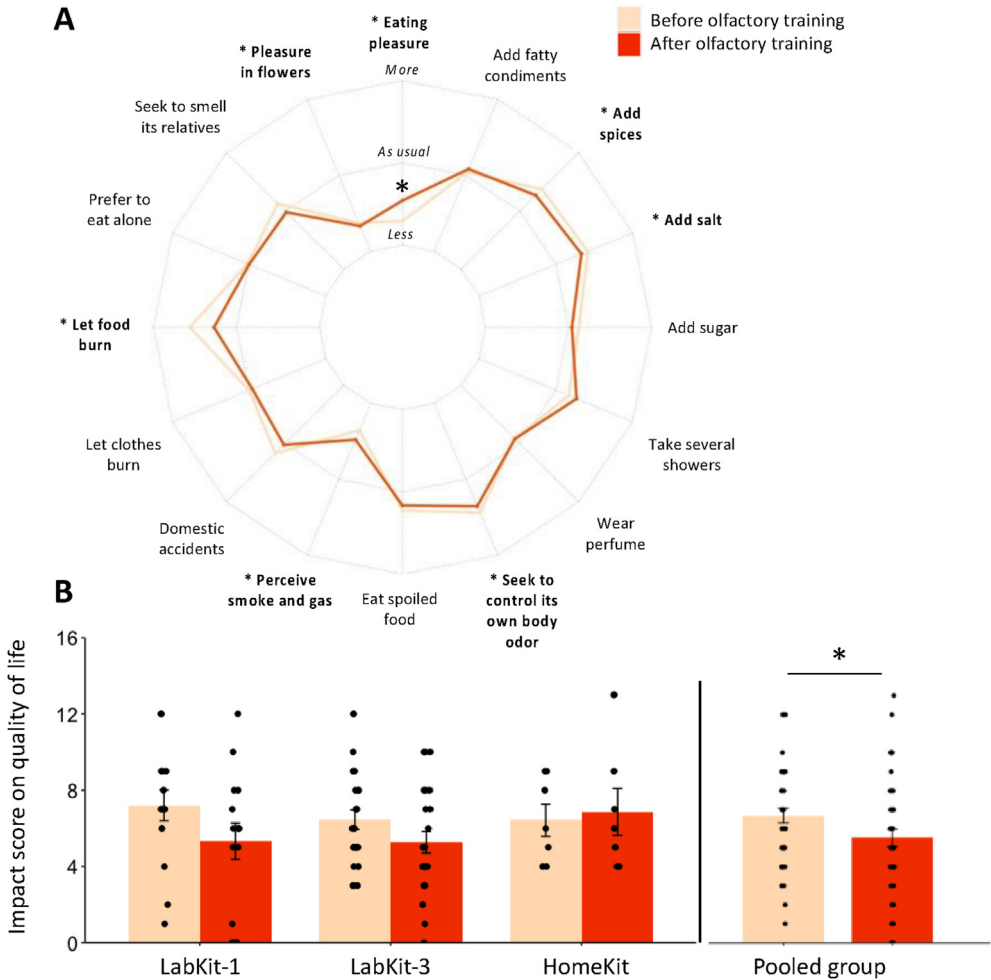


Figure 4. The impact of olfactory disorder on quality of life is reduced by olfactory training.

A) Radar chart of mean response for each item of the olfaction-related quality of life questionnaire before and after olfactory training (12 weeks). For each item, the mean response is represented on the following scale: “more” (outer periphery of the circle), “as usual” (intermediate zone), “less” (inner periphery of the circle). The items in bold are the ones that were significantly different from “as usual” before olfactory training (Wilcoxon test with Bonferroni correction). After olfactory training, only eating pleasure was significantly different from before training (Wilcoxon test with Bonferroni correction). B) Impact score of olfactory disorders on quality of life before and after olfactory training for LabKit-1, LabKit-3 and HomeKit olfactory training protocols and pooled group. Data are expressed as mean±SEM. Dots represent individual participants. ANOVA followed by post-hoc t-test with Bonferroni correction. * $P<0.05$. $n=18$ for LabKit-1, $n=26$ for LabKit-3, $n=7$ for home-Kit, $n=51$ for pooled group.

Discussion

The main aim of this study was to improve the management of olfactory disorders. To this end, we set up a screening test, and compared the performance of 3 training protocols in post-COVID-19 patients suffering from persistent smell deficits. The screening tool was designed for both clinical and self-administration use, and training regimens included solutions to overcome the problems of adherence, standardization and monitoring of olfactory training. In addition, in response to poor accessibility during the sanitary crisis, we explored the interest of olfactory training based on home-products. Lastly, we evaluated the benefits of these olfactory training regimens on quality of life.

For **olfactory screening**, quick tests were proposed such as a reduced version of the Sniffin' Sticks identification test [34], the Q-sit [35] or the Scentinel test [36]. In our study, we developed a test based on the scratch and sniff card principle [7] that enabled to distinguish olfactory statuses and its scores were positively correlated to the ETOC-16 scores. The predictive model built had a moderate sensitivity of 70% and may improve with a higher number of odors (4 scented cards here). On the other hand, the specificity of 84% was not of high concern as this tool is not designed to distinguish hyposmia from anosmia, but rather to identify patients with potential olfactory loss in a quick and dirty manner before sending them for a more complete diagnostic. In addition, this tool performed well in discriminating anosmics from normosmics suggesting that most of the prediction errors arise from participants with borderline performance (weak dysosmia). Moreover, using an odorless blank card, we showed that the perceived intensity rating, is not subject to different use from the response scale between dysosmics and normosmics. Therefore, despite being subjective, perceived intensity rating seems a reliable measure, implying a potential omission of a blank stimulation in future tests. It is important to keep in mind that sample sizes were small and that the cross-validation approach, despite making full use of the data, does not test the model on an independent group of participants. Therefore, this tool remains to be tested in larger and independent samples. Overall, the screening test is a quick (about 5min to complete), easy to use (scratch and sniff), with a one-time use support and long-term conservation, making it suitable for clinical and perhaps self-administered practice.

Regarding olfactory training, **maintaining treatment** adherence posed a challenge [37]. In the best-case scenario, when a drop in motivation does not lead to leaving the study, it causes several missed training sessions. 69% of patients performed all three visits (73% without the HomeKit group), close to a previous study (64%) with patients of several etiologies [32]. This slightly higher compliance might be explained by the use of feedback during training, but overall remains unsatisfactory. Indeed, most studies set up a follow-up consisting of regular phone calls [20] or asking patients to keep a diary [38,39] to record their assiduity during training. Among other studies, compliance (corresponding to compliance plus assiduity as defined here) ranged from 55% to 88% [37,40,41] and the use of an olfactory ball (63%) [42] or the follow up by a physiotherapist (88%) [43] were shown to improve compliance. The lower assiduity in HomeKit is probably due to the fact that giving a training kit to patients empower them toward the protocol and/or they feel better taken care of. These results suggest that the best way to maximize compliance might be to provide close support to patients, for which physiotherapists or speech therapists are good candidates.

Evolution of **olfactory performances** was followed in post-COVID-19 patients, along 3 different olfactory training protocols of 12 weeks duration. Patients displayed an overall improvement in olfactory performance irrespective of the protocol, suggesting that increasing daily odor exposition did not increase olfactory training efficacy. Similar results were reported for a shorter (4 weeks) and a longer (16 weeks) training duration [44,45]. Furthermore, our data showed that assiduity was associated with olfactory progression, suggesting that patients who experienced progression are more likely to follow the protocol, and/or that training quantity/regularity leads to better outcome, highlighting the relevance to find ways of maximizing assiduity. Interestingly, HomeKit allowed some patients to recover their olfaction (29%), even though this regimen remains highly variable due to patients' choices of scented products. We conclude that autonomous approaches to training with adapted instructions remain an option when it is not possible to supply a kit.

One of the limitations of our protocol is that we chose not to include a group of patients performing odorless training. Over and above the ethical reasons, we found it difficult to compare results from a group of patients who smell real odors with a group who smell nothing, at the risk of giving rise to a

feeling of non-improvement in the latter. In any case, in our study, 59% of patients (LabKit-1: 12/18, LabKit-3: 16/26, HomeKit: 2/7) displayed a clinically significant improvement in olfactory performances during training. In post-infectious olfactory disorders, spontaneous recovery is about 6% within 12 weeks [20] and increases to 32–35% of patients within one year [46,47]. For classical 12 weeks-long olfactory training intervention, recovery rate ranges between 21–56.3% [20,25,48,49]. When looking specifically at the post-COVID-19 etiology, spontaneous recovery is close to post-infectious olfactory disorders (6%) [50] and recovery following training ranges from 10.9–40% [50–52] (See [supplementary Figure 3](#)). Therefore, the recovery rate in this study is positioned at the upper range of training studies in both post-infections and post-COVID-19 olfactory disorders and appears higher than spontaneous recovery. We can thus reasonably conclude that LabKit and HomeKit training protocols improved olfaction. It is also important to note that our criteria for clinically significant improvement may not catch the same olfactory evolution as other studies, since the ETOC-16 diagnosis test contains a detection/localization task and no threshold/discrimination tasks, contrary to the Sniffin'Sticks.

Another result of interest was that initial olfactory performances were negatively correlated to progression, which is in accordance with retrospective studies highlighting that patients with low baseline olfactory function were more likely to display significant progression after training [53–55]. One explanation is that the sensitivity range of the ETOC-16 test is higher for low performances, and thus improvements are more likely to be detected when starting from low performances. One question that may be raised is how can we improve the training protocol? Since olfactory stimuli coupled to congruent visual labels enhanced olfactory training efficacy [32], multi-sensory integration may be implemented through web-based training to improve efficacy [56]. Odorant renewal during training is also a relevant optimization option [25]. Flavor-based training improved retro-nasal olfactory performances with a high compliance rate and thus could be considered as a complement to conventional training with potentially enhanced eating pleasure [57].

Finally, to examine whether olfactory improvements could enhance living conditions, we explored different **quality of life** domains. In line with previous studies [5], patients were initially affected in hedonic perception, danger signal detection, hygiene regulation and food habits. Independently from training regimens, impact on quality of life was reduced after training, as previously reported for dysosmic patients of various etiologies [32]. Regarding food habits, post-COVID-19 patients tend to use more salt and spices, similar to compensation mechanisms previously described in dysosmics [3,5]. Among all items, eating pleasure seems to be particularly improved by olfactory training, despite not returning to pre-infection level. This finding is consistent with the fact that smells are important for food enjoyment and food pleasantness important for well-being [5]. Here, nutritionists and dieticians could contribute to restoring eating pleasure in dysosmics by proposing a diet focusing on textures, visual and trigeminal sensations, etc. while also maintaining a balanced nutritional intake.

Conclusion

To improve management of olfactory disorders, we have developed a new olfactory test that has shown acceptable performance for rough screening purposes. We proposed different approaches to olfactory training on post-COVID-19 patients and found that the number of odors smelled daily did not seem to improve efficacy. The use of a web platform allowed us to monitor and standardize olfactory training administration, but compliance and assiduity remained relatively low; there is still an overall need for strategies to improve this in olfactory training paradigms. To promote access to care, training with home-products remains a feasible option but requires improvements in compliance. Finally, we found that these olfactory training protocols improved quality of life that was initially impaired by olfactory disorders, particularly in eating pleasure.

Statement of authorship

Study design and concept: Ferdenzi C. and Bensafi M. Screening and Training support development: Fournel A. and Bensafi M. Hospital/laboratory relay: Daude C, Ferdenzi C. Data collection: Bellil D, Degraix J, Faure F, Fioux M, Idriss S, Denoix L Data compilation: Moussy E, Daude C. Analysis and

interpretation of data: Moussy E, Ferdenzi C, Bensafi M, Richard M. Drafting of the article: Moussy E., Richard M, Bensafi M, Ferdenzi C. Final approval of the article: all authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nutos.2024.05.007>.

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