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Olfactory perceptual fingerprints of people with olfactory dysfunction and healthy controls

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Abstract

Objective(s): An olfactory perceptual fingerprint (OPF) defines one's olfactory perception using perceptual descriptor ratings (such as odor pleasantness, intensity) for a set of odors. OPFs have been shown to distinguish patients with COVID-related olfactory dysfunction (OD) and healthy controls with 86% accuracy. However, all participants rated the same odorants. With the aim to evaluate whether the OPFs are indeed odorant independent, previously published dataset by Lötsch et al. was reanalyzed. Furthermore, this independent dataset was used to check whether the OPFs separate patients with OD due to various causes from controls.

Methods: The study included 104 controls and 42 patients, who were randomized into four odor sets with 10 odorants each. Odorants were presented using a computer-controlled olfactometer and evaluated on scales from 1 (*not at all*) to 5 (*very*) using perceptual descriptors pleasant, intensive, familiar, edible, irritating, cold/warm, and painful.

Results: Permutational multivariate analysis of variance showed that the odor set did not have a significant effect on the OPFs, confirming that the OPFs are indeed odorant independent. On the other hand, both diagnosis and age affected the OPFs ($p < .001$) and explained around 11% and 5% of the variance of the OPFs, respectively. Furthermore, a supervised machine learning method, random forest classifier, showed that OPF can distinguish patients and controls with 80% accuracy.

Conclusion: OPFs are odorant independent. Patients perceived odors as less familiar, less intense, and less edible than controls. Other perceptual descriptors were much less important for the separation of patients and controls.

Level of evidence: 3

KEYWORDS
olfaction, olfactory dysfunction, olfactory perception, olfactory perceptual fingerprint, smell

1 | INTRODUCTION

Sense of smell starts with odorants binding to the olfactory receptors. Sensory detection then enables perceptual interpretation of odors, for example as pleasant or unpleasant, intense or weak, and familiar or unfamiliar.[1,2]

It is estimated that around 20% of people have a decreased sense of smell.[3] Their olfactory function is evaluated using odor threshold, discrimination, and identification, all of which decline when olfactory dysfunction (OD) develops.[4–6] However, much less is known about their olfactory perception. A measure of olfactory perception is an olfactory perceptual fingerprint (OPF), which defines one's olfactory perception using perceptual descriptor ratings (such as odor pleasantness, intensity, familiarity) for a set of odors. Secundo et al.[7] defined an odor specific, but descriptor independent OPF, where individual's perception was characterized using a matrix of perceived odor similarity. Later, Snitz et al.[8] defined a descriptor specific, but odor independent OPF, where individual's perception was characterized using a N-dimensional vector when *N* is the number of perceptual descriptors. In a previous study, patients with OD due to Coronavirus disease (COVID-19) were shown to perceive odors as less familiar and less intense than controls.[9] Furthermore, the OPFs as suggested by Snitz et al. were able to distinguish patients with COVID-related OD from healthy controls with accuracy of 83% using an unsupervised machine learning method and an accuracy of 86% using a supervised machine learning method.[9] However, participants rated the same odorants although in theory one could use different sets of odorants.

With the aim to evaluate whether the OPFs are comparable when participants rate different odorants, previously published dataset by Lötsch et al.[10] was reanalyzed. Furthermore, this independent dataset was used to check whether the OPFs still separate patients with OD from healthy controls.

2 | MATERIALS AND METHODS

2.1 | Participants

Dataset from Lötsch et al.[10] was reanalyzed to study the OPFs. Controls with normal self-rated olfactory function and patients with OD were included. Controls were recruited through flyers and patients were recruited at the outpatient clinic of the Smell & Taste Clinic, Department of Otorhinolaryngology, TU Dresden. All participants gave informed written consent. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the University Clinic of the TU Dresden (application number: EK 390102014).

Participants had to be 18 years or older. Exclusion criteria were smoking, pregnancy, and neurodegenerative disease (such as Parkinson disease or Alzheimer disease). Patients were included if they were hyposmic or anosmic based on the threshold, discrimination and identification (TDI) score as explained below.

Control's olfactory function was evaluated using the 16-item odor identification (I) task. If the identification score was above 12, they were diagnosed as normosmic, if it was between 12 and 8, they were hyposmic and if the score was below 8, they were anosmic.[4] Patients underwent a thorough clinical evaluation including a structured medical history and otorhinolaryngological examination. Patients' olfactory function was evaluated using the extended Sniffin' Sticks test battery, which yields odor threshold (T), discrimination (D), and identification (I) scores.[4,6] These three scores were then summed into the TDI score. If the TDI was 30.75 and above, they were diagnosed as normosmic and were excluded. If the TDI was in the range between 16.25 and 30.5, they were hyposmic and if the TDI was below 16, they were anosmic.[4,6] Participants also underwent the Montreal Cognitive Assessment, a screening tool for mild cognitive impairment.[11]

2.2 | Perceptual ratings of the odorants

Odorants were chosen to represent the multidimensionality of odors in chemical, olfactory, and trigeminal space and grouped into four sets of 10 odorants (Table 1). They were prepared to be isointense as described in the article by Lötsch et al.[10]

Odorants were presented using a computer-controlled olfactometer with the total flow rate of 2 L/min. They were presented birhinally using a flexible polyurethane tube, which was inserted 1 cm into the nasal cavity to reach beyond the nasal valve area. To monitor breathing (AWM2100V, Honeywell, MN, USA) an additional nasal cannula (AirLife™, inner diameter of the tube: 2.8 mm) was used. Odors were presented for 5 s at the beginning of an inspiration phase. The sequence of odor presentation was randomized, and each odor was presented three times at an interval of 40–60s. After presentation, participants were asked to rate the odor on discrete scales from 1 to 5 using perceptual descriptors pleasant, intensive, familiar, edible, irritating, cold/warm, and painful. The scales were labeled as follows (left—right): pleasant ("how much do you like the odor": "very unpleasant"—"very pleasant"), intensive ("how intense is the odor": "barely perceptible"—"very intense"), familiar ("how familiar are you with the odor": "not familiar at all"—"very familiar"), edible ("how much would like to eat something that smells like this": "not at all"—"very much"), irritating ("how irritating do you find the odor": "not at all irritating"—"very irritating"), cold/warm ("how cold/warm do you find the odor": "very cold"—"very warm"), and painful ("how painful do you find the odor": "not painful at all"—"very painful"). Of note, not all ratings were made after each presentation.

2.3 | Olfactory perceptual fingerprint

An OPF was calculated as suggested by Snitz et al.[8] Each participant *m* rated *M* (=10) odors using *N* (=7) descriptors. First, the differences between their rating for the odor *i* using the descriptor *j* versus the mean rating for the same odor *i* using the same descriptor *j* among

TABLE 1 Odorants included in each odor set, their trivial name, CAS (Chemical Abstract Service reference number), CID (PubChem Compound Identification), concentration, and their quality are shown.

Odor set	Controls, patients	Trivial name	CAS	CID	Quality	Concentration
1	30 controls 8 patients	Isoamylacetate	123-92-2	31,276	Banana, pear	0.032
		Cineol	470-82-6	2758	Eucalyptus	0.5
		Geraniol	106-24-1	637,566	Fruity, rose	Neat
		Methylsalicylate	119-36-8	4133	Bubble gum, wintergreen	7.26
		trans-Anethole	4180-23-8	637,563	Liquorice, anise	4.17
		Ethylacetate	141-78-6	8857	Sweet, "pear drops"	10
		Propionic acid	79-09-4	1032	Stinging, vinegar, acidic	0.041
		Eugenol	97-53-0	3314	Clove	Neat
		2-Nonanon	821-55-6	13,187	Fruity, cheesy	1
		Indole	120-72-9	798	Sweet, unpleasant	0.161
2	24 controls 9 patients	Benzaldehyde	100-52-7	240	Marzipan, cherry, almond	0.015
		Butyiric acid	107-92-6	264	Rancid butter, parmesan cheese, vomit	0.001
		p-Cresole	106-44-5	2879	Livestock waste	0.018
		Guajacole	90-05-1	460	Band aid, sweet, creamy	2.09
		(+)-Linalool	126-90-9	6549	Lemon, lime	2.17
		(+)-Fenchone	4695-62-9	1,201,521	Minty, camphor-like	Neat
		3-Hydroxy-3-methylhexanoic acid	58,888-76-9	16,666,688	Sweaty	0.01
		Amylcaproate	540-07-8	31,266	Banana, fruity	0.56
		2,3-Butandione	431-03-8	650	Butter, perspiration	3E-05
		Citronellal	106-23-0	7794	Lemon	0.014
3	25 controls 17 patients	*cis*-3-Hexenol	928-96-1	5,281,167	Grass	0.002
		1-Butanol	71-36-3	263	Cheese, sweat	Neat
		4-Ethyloctanoic acid	16,493-80-4	61,84	Goaty	Neat
		β-Jonone	79-77-6	638,014	Lilac	7.27
		2-Methylpropanal	78-84-2	6561	Wet cereal or straw	1E-06
		Terpinene-4-ol	562-74-3	11,230/5,325,830	Musty	Neat
		Isobutyric acid	79-31-2	6590	Rancid butter	1
		4-Decanolid	706-14-9	12,813	Peachy	10
		Citronellol	106-22-9	8842	Lemony	17.85
		3-Methyl-3-sulfanylhexan-1-ol	307,964-23-4	10,130,039	Sweaty	0.01
4	25 controls 8 patients	D-(+)-Limonene	5989-27-5	440,917	Lemony	Neat
		Alpha-Pinene	80-56-8	440,968	Woody, pine, resinous	Neat
		Methional	3268-49-3	18,635	Potato	0.001
		Benzylacetate	140-11-4	8785	Yasmin, fruity, ylang	1.55
		1-Octen-3-ol	3391-86-4	18,827	Mushrooms	0.56
		trans-2-Hexenylacetate	2497-18-9	17,243	Fruity, apple, waxy	10
		L-Carvone (−)	6485-40-1	439,57	Caraway	Neat
		Beta-Caryophyllene	87-44-5	5,281,515	Peppery, spicy, resinous	Neat
		Heptanal	111-71-7	8130	Fruity, sharp	1
		2-Butanone	78-93-3	6569	Cheese	0.01

Note: The number of patients and controls included in each odor set is also reported.

$$(p_m)_j = \frac{\sum_{i=1}^{M}(p_{i,j} - \bar{p}_{i,j})}{M}$$

FIGURE 1 Equation for one coordinate (or one perceptual descriptor *j*) of the olfactory perceptual fingerprint for a participant m. Participant *m* rates *M* odorants. $p_{i,j}$ is the participant's rating for odorant *i* long a descriptor *j*. $\bar{p}_{i,j}$ is the average rating for odorant *i* along a descriptor *j* among the controls.

the controls were calculated. After that each participant was described by an $M \times N$ matrix of relative scores for each descriptor and each odor. Next, *M* relative scores were averaged along each of the descriptors *N*. In the end, each participant was described by a seven-dimensional vector, the OPF. The formula for calculation of one coordinate of an OPF is shown in Figure 1.

2.4 | Statistical analysis

In the publication by Lötsch et al.[10] missing perceptual ratings were imputed for subjects who had at least two thirds of perceptual descriptor ratings per odor. They were imputed using *k*-nearest neighbors with $k = 3$ within the odor set using the R-library *DMwR*.[12] Here analysis was conducted on the imputed dataset.

Median and interquartile range were used to describe the central tendency and variance of continuous variables. Nonparametric Mann–Whitney test was used to compare non-normally distributed continuous variables among patients and controls. Frequencies were used to describe the distribution of categorical variables and χ^2 tests were used to compare categorical variables, such as gender. Kruskal–Wallis analysis of variance was used to compare non-normally distributed continuous variables among the four odor sets. OPFs were calculated as explained above. A *p*-value of <.05 was considered statistically significant.

To evaluate the effect of the odor set, diagnosis, and age on the OPFs, a permutational multivariate analysis of variance (PERMANOVA) was performed. Dependent variables were the OPFs. Independent variables were the odor set (four levels: 1,2,3,4), diagnosis (two levels: control, patient), and age (two levels: <55, more than 55). PERMANOVA with 999 permutations was applied on the Euclidian distance matrix of the OPFs using an *adonis2* function from the *vegan*[13] package.

In the exploratory analysis of the effect of the cause of the OD on the OPFs, another PERMANOVA was performed on the OPFs of patients with postviral and idiopathic OD. Dependent variables were the OPFs. Independent variables were the cause (two levels: postviral, idiopathic), duration (two levels: less than 6 months, more than 6 months), age (two levels: less than 55, more than 55), odor set (four levels: 1, 2, 3, 4), and gender (two levels: male, female). PERMANOVA with 999 permutations was applied on the Euclidean distance matrix of the OPFs using an *adonis2* function from the *vegan*[13] package.

Next, two machine learning methods were used to check whether the OPF can predict olfactory function. In other words, whether one can classify an individual as a control, or a patient based on their olfactory perception.

An unsupervised machine learning method, hierarchical cluster analysis of the OPFs, was performed using Ward's method on Euclidean distances. The function *hclust* was used. An R package *NbClust*[14] was used to find the best number of clusters. A circular dendrogram was created using the R package *factoextra*.[15] Kruskal–Wallis analysis of variance was used to compare non-normally distributed continuous variables among the three clusters. For post hoc analysis, Dunn test with Bonferroni corrections were performed.

Next, a supervised machine learning method, random forest classifier on the OPFs (and a second one on the "quick-OPF") was trained. A function *randomForest* from an R package *randomForest*[16] was used. Due to imbalanced dataset, stratified sampling using a function *initial_split* from a package *rsample*[17] was performed to split the dataset into training and testing in the ratio of 2:1. Random forest classifier was trained on the training dataset with hyperparameters at 200 trees and 2 randomly selected features as candidates at each split. The model was evaluated on the testing dataset using a confusion matrix (package *caret*[18]). Permutational importance was used to evaluate, which perceptual descriptors were the most important for the separation of patients and controls.

All statistical analyses were performed using R Statistical Software[19] (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) with additional packages for data manipulation and visualization *tidyverse*,[20] and *gghalves*.[21]

3 | RESULTS

The study by Lötsch et al. included 104 healthy controls and 42 patients with OD (Table 2). As can be seen, patients were older and had a lower olfactory function than controls. Further analysis showed that there was no difference among the four odor sets (Table S1). A thorough analysis of olfactory perception for each odorant can be found in the original publication by Lötsch et al.[10] Here, olfactory perception was further analyzed using OPFs.[8] The overall design, idea, and results of this study are shown in Figure 2. First, individual OPFs were calculated based on the perceptual descriptor ratings. The seven components of the OPFs (pleasant, intensive, familiar, irritating, edible, cold/warm, and painful) for controls and patients are plotted as violin plots and boxplots on Figure 3. As can be seen, patients perceived odors as significantly less intense, less familiar, and less edible compared with controls. Correlations among the OPF components are shown in the Figure S1.

The first aim was to evaluate whether the OPFs are independent of the odor set. PERMANOVA showed that the odor set did not have a significant effect on the OPFs, confirming that OPFs are independent of the odor set. On the other hand, both diagnosis (patients and controls) and age (≤55 and >55 years) affected the OPFs ($p < .001$) and explained around 11% and 5% of the variance of the OPFs, respectively (Table 3).

TABLE 2 Age, gender, olfactory function, and MoCA score of healthy controls and patients with olfactory dysfunction.

	Median (interquartile range) or *N* (%)		
	Controls (*N* = 104)	**Patients (*N* = 42)**	***p*-Value**
Age	28.0 (24.0–39.0)	56.5 (44.3–62.8)	**<.001**
Gender (male: female)	39 (38%): 65 (62%)	13.0 (31%): 29 (69%)	.58
TDI	/	23.3 (20.2–27.6) [2]	/
Threshold	/	2.4 (1.0–4.8) [10]	/
Discrimination	/	9.0 (7.8–12) [10]	/
Identification	13.0 (13.0–14.0)	11.0 (9.0–11.8) [8]	**<.001**
Diagnosis			
Normosmia	93 (89%)[a]	0 (0%)	/
Hyposmia	11 (11%)[a]	41 (97%)[b]	/
Anosmia		1 (3%)[b]	/
MoCA	28.0 (27.0–29.0)	27.0 (25.3–28.0)	**<.001**
Cause			
Viral	/	18 (43%)	/
Head trauma	/	4 (10%)	/
Sinonasal disease	/	4 (10%)	/
Surgery	/	2 (5%)	/
Idiopathic	/	12 (29%)	/
Other	/	2 (5%)	/
Duration of the OD (months)	/	14.0 (7.8–18.0)	/

Note: For patients the cause of olfactory dysfunction and its duration are also shown. [] is the number of people with missing values. Significant values are shown in bold.
Abbreviation: MoCA, montreal cognitive assessment.
[a]Based on the identification score.
[b]Based on the TDI score. Two with the missing TDI score were determined based on the identification score.

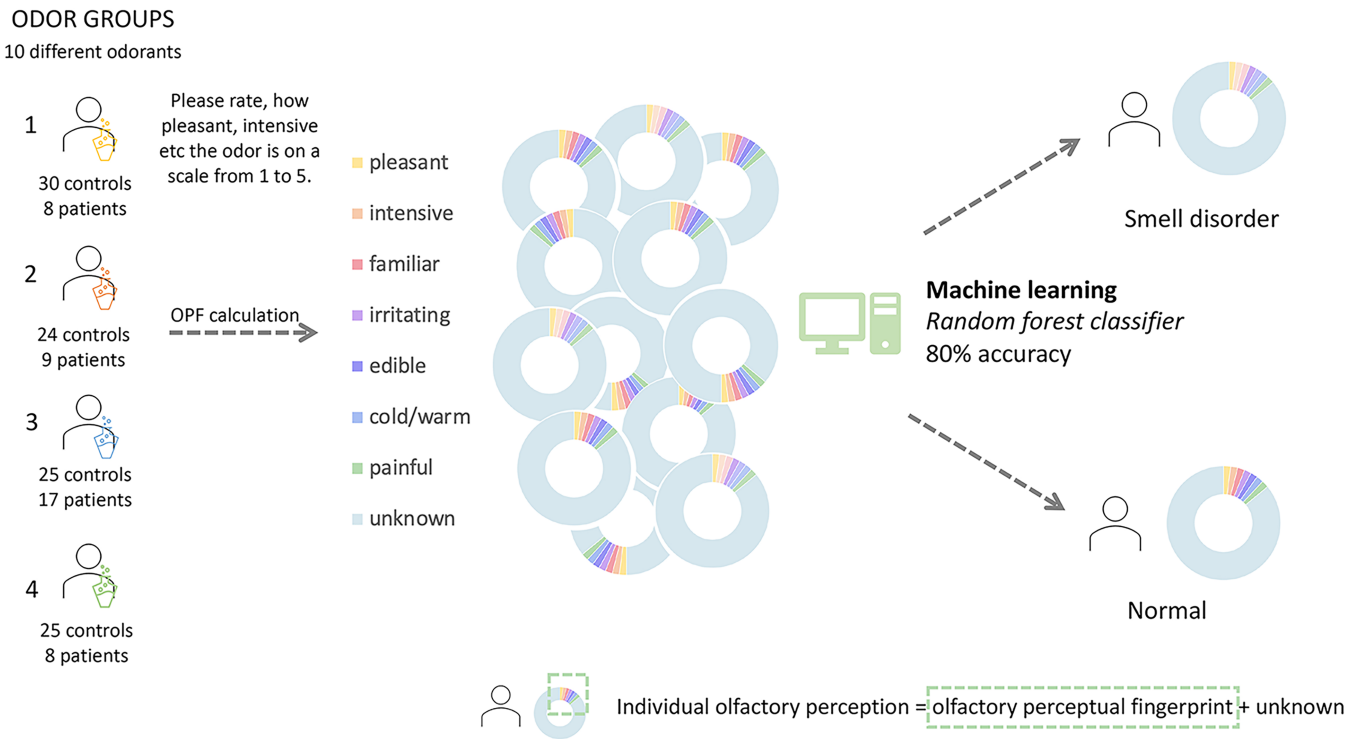

FIGURE 2 Visual presentation of the study and its results. OPF, olfactory perceptual fingerprint.

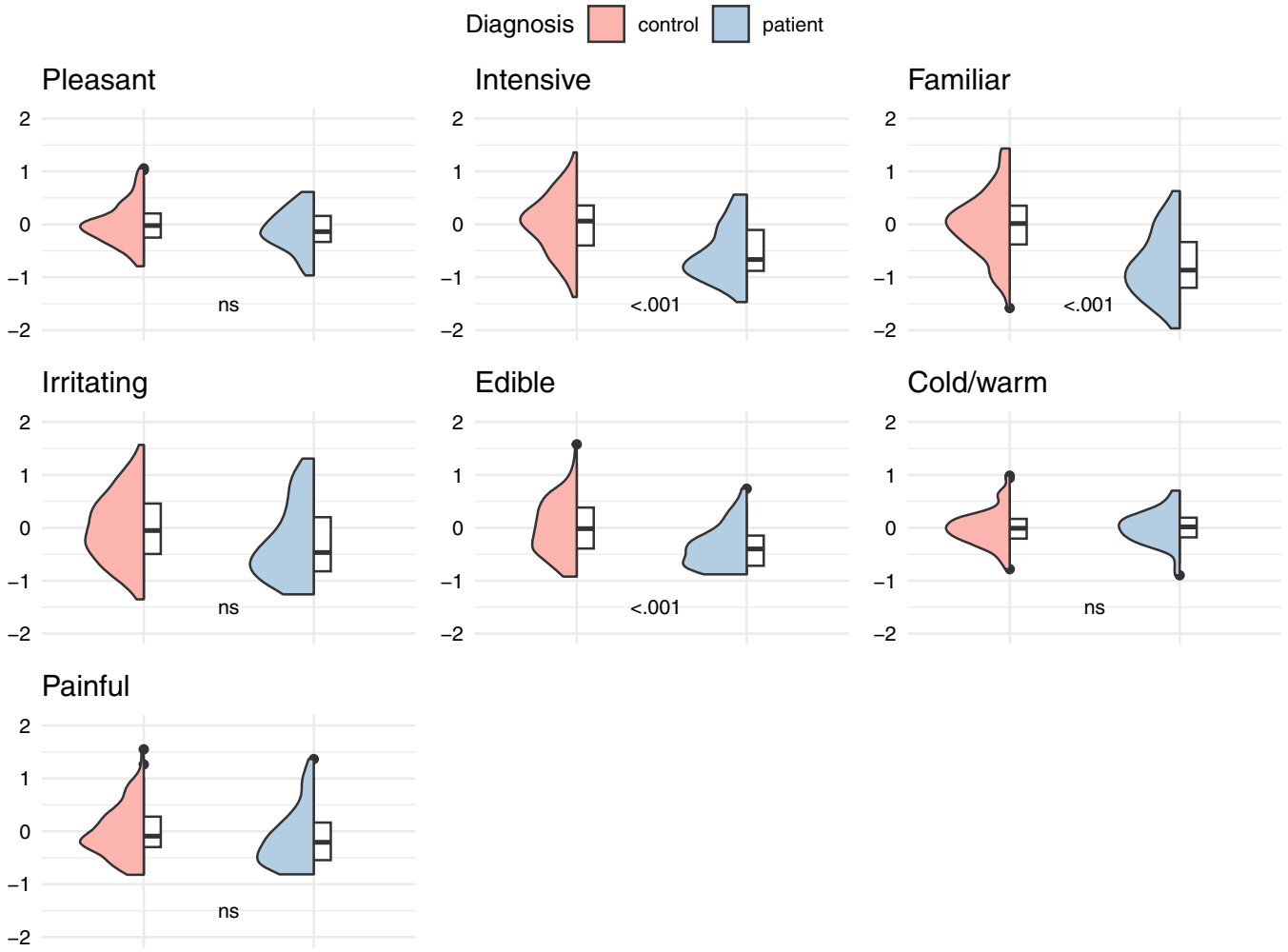

FIGURE 3 Components of the olfactory perceptual fingerprints (perceptual descriptors—pleasant, intensive, familiar, irritating, edible, cold/warm, painful) among healthy controls (pink, $N = 104$) and patients with olfactory dysfunction (blue, $N = 42$). Adjusted p-values using a Bonferroni correction are reported.

TABLE 3 PERMANOVA results with the degrees of freedom (Df), sum of squares, partial R^2, pseudo-F statistic, and p-value.

Independent variables	Df	Sum of squares	R^2	F	p-Value
Odor set (1, 2, 3, 4)	3	2.6	0.009	0.49	.896
Diagnosis (patient, control)	1	32.5	0.11	18.2	**.001**
Age (<55, more than 55)	1	13.7	0.05	7.7	**.001**
Residual	140	250.1	0.83		

Note: Dependent variable were the olfactory perceptual fingerprints (pleasant, intensive, familiar, irritating, edible, cold/warm, painful). Independent variables were odor set (four levels: 1,2,3,4), diagnosis (two levels: control, patient), and age (two levels: less than 55, more than 55). Significant values are shown in bold.

Abbreviation: PERMANOVA, permutational multivariate analysis of variance.

Although the PERMANOVA already showed that the OPFs differ among healthy people and patients with OD, other methods were used to further investigate whether the OPFs can predict olfactory function. First, an unsupervised machine learning method, hierarchical cluster analysis of the OPFs was performed. "NbClust" suggested three clusters (Figure 4). In the first cluster, there were 32 controls and 30 patients. In the second cluster, there were 32 controls and 1 patient. In the third cluster, there were 40 controls and 11 patients. To further understand how participants were clustered, controls and patients in the three clusters were compared (Table 4). Controls, which were clustered with the majority of the patients in the first cluster, were older than controls in the other two clusters. However, there was no difference in their olfactory function measured using a 16-item identification test.[4]

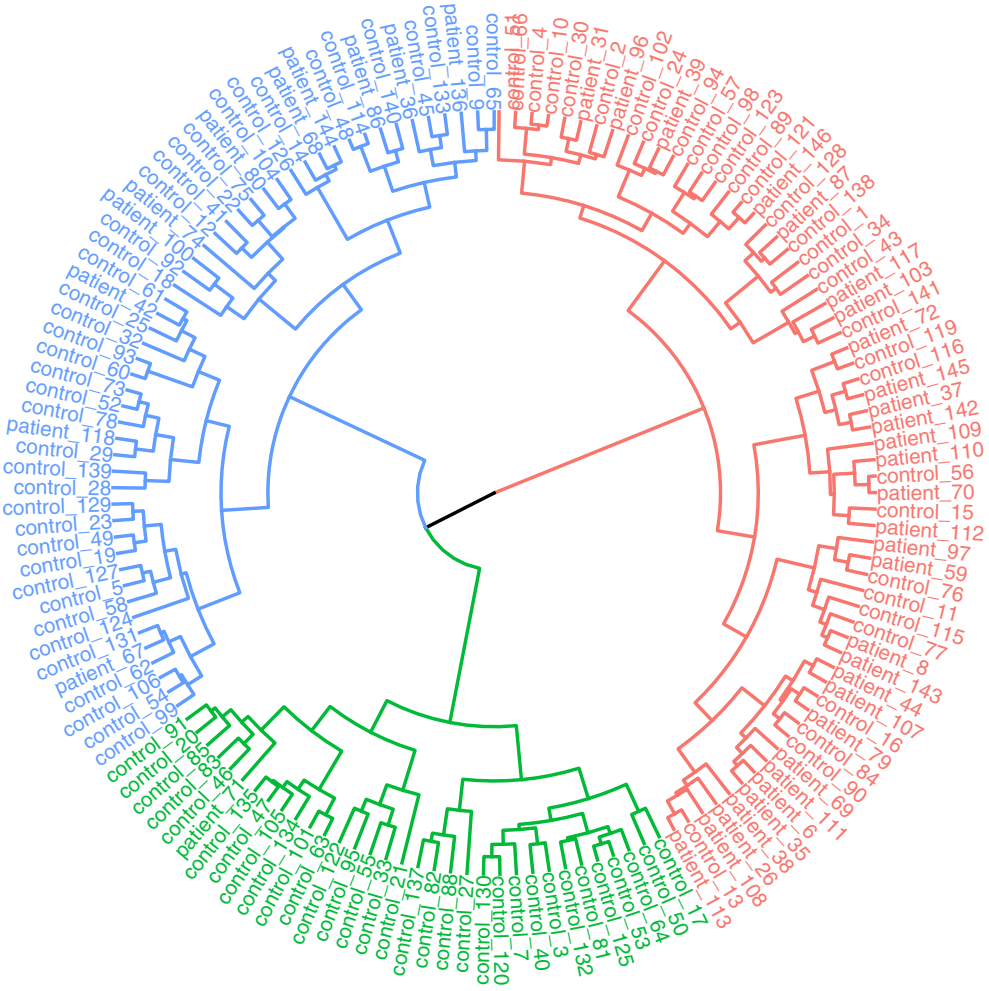

FIGURE 4 A circular dendrogram from hierarchical cluster analysis of the olfactory perceptual fingerprints using Ward method on Euclidean distances. In the first cluster (orange), there were 32 controls and 30 patients. In the second cluster (green), there were 32 controls and 1 patient. In the third cluster (blue), there were 40 controls and 11 patients.

TABLE 4 Age, gender, and olfactory function of the controls and patients clustered together using hierarchical cluster analysis.

	Controls			
	Cluster 1	**Cluster 2**	**Cluster 3**	
	***N* = 32**	***N* = 32**	***N* = 40**	***p*-Value**
Age (years)	37.5 (26.8–63.8)	25.0 (23.0–28.0)	28.0 (24.0–36.0)	**<.001**
Gender (male:female)	12 (38%):20 (62%)	13 (41%): 19 (59%)	14 (35%): 26 (65%)	.89
Identification	13.0 (12.0–14.0)	14.0 (13.0–15.0)	14.0 (13.0–14.0)	.12
Odor set (1:2:3:4)	11 (34%):5 (16%):8 (25%):8 (25%)	7 (22%):8 (25%):9 (28%):8 (25%)	12 (30%):11 (36%):8 (20%):9 (23%)	.85
	Patients[a]			
	Cluster 1	**Cluster 2**	**Cluster 3**	
	***N* = 30**	***N* = 1**	***N* = 11**	
Age (years)	59.0 (45.5–65.5)		55.0 (44.0–58.0)	.19
Gender (male:female)	10 (33%): 20 (66%)		2 (18%): 9 (82%)	.58
TDI	24.0 (20.8–27.8)		20.5 (18.3–26.5) [2]	.18
Threshold	2.5 (1.1–4.8) [7]		2.0 (1.0–4.0) [2]	.70
Discrimination	9.0 (8.0–11.5) [7]		9.0 (7.0–12.0) [2]	.61
Identification	11.0 (9.5–12.0) [7]		9.0 (8.5–11.0)	.05
Odor set (1:2:3:4)	7 (23%):5 (17%):13 (43%):5 (17%)		1 (10%):3 (27%):4 (36%):3 (27%)	.60

Note: [] is the number of people with missing values. Significant values are shown in bold.
[a]Among patients only patients in clusters 1 and 3 were compared as cluster 2 included only one patient.

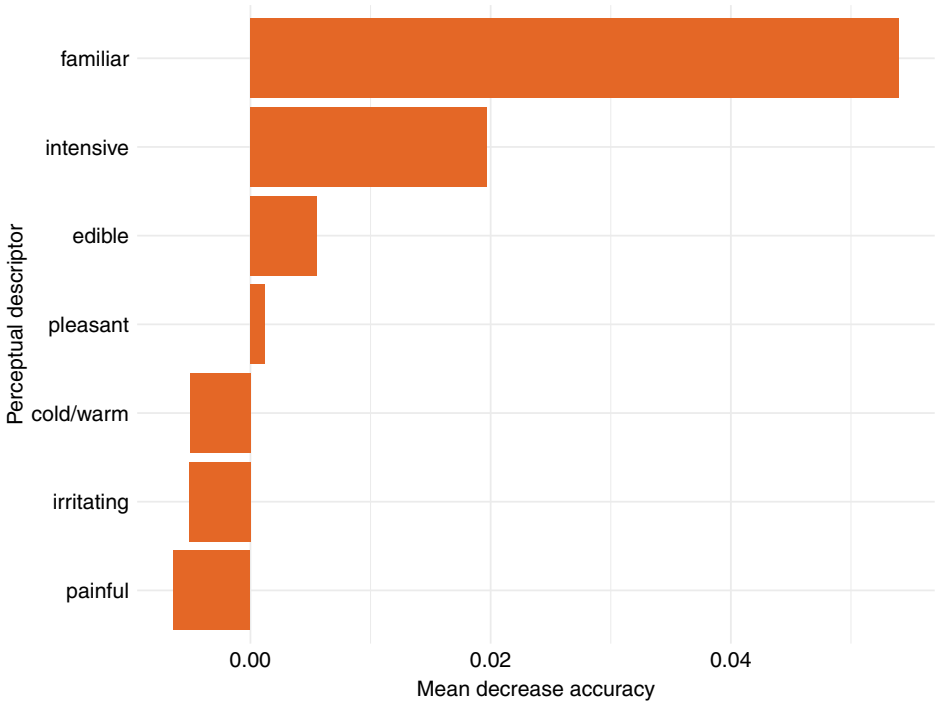

FIGURE 5 Variable importance of a random forest classifier trained on the olfactory perceptual fingerprints (calculated using perceptual descriptors pleasant, intensive, familiar, irritating, edible, cold/warm, painful) to distinguish patients ($N = 42$) and controls ($N = 104$).

Next, a supervised machine learning method, random forest classifier, was trained on the OPFs of 2/3 of the controls and 2/3 of the patients. Out of bag error rate was 33%. The remaining 1/3 of the controls and 1/3 of the patients were used to test the model and its accuracy on this testing dataset was 80% (95% CI: 66%–90%). Furthermore, sensitivity and specificity for separating patients and controls were 57% and 89%, respectively. As can be seen from the variable importance in Figure 5, the most important perceptual descriptors were odor familiarity and intensity.

As only three components of the OPFs (odor familiarity, intensity, and edibility) were significantly different among patients and controls, another random forest classifier was trained on the OPFs using only these three components ("a quick-OPF"). It was trained on the "quick-OPFs" of 2/3 of the controls and 2/3 of the patients. Out of bag error rate was 26% and accuracy on the testing dataset was 84% (95% CI: 70%—93%). Furthermore, sensitivity and specificity for separating patients and controls were 71% and 89%, respectively. Again, variable importance was checked (Figure S2).

Additionally, as odor familiarity and odor intensity were by far the most important components of the OPFs, a scatter plot of these two components is shown in Figure S3. Indicating that only odor familiarity and odor intensity already to some extent separate patients and controls.

In the exploratory analysis, we investigated if the OPF among patients differed in relation to the cause of OD. Patients with different causes were included in the study, and unfortunately most groups included less than five patients. Therefore, for this analysis only patients with postviral ($N = 18$) and idiopathic ($N = 12$) OD were included. Exploratory PERMANOVA showed that among patients with postviral and idiopathic OD, the cause did not have a significant effect on the OPFs (Table S2).

4 | DISCUSSION

OPFs have been shown to distinguish patients with COVID-related OD and healthy controls with 86% accuracy when using a random forest classifier.[9] However, participants rated the same odorants. This study adds that the OPFs are odorant independent and can be compared if using the same perceptual descriptors but different odorants. Furthermore, this independent dataset confirmed that the OPFs distinguish patients with OD from controls with 80% accuracy, which appears to be independent of the cause of OD. In line with previous results[9] odor familiarity and intensity were by far the most important for the separation.

Interestingly, the analysis of the individual perceptual ratings of the 40 odors in the original publication by Lötsch et al.[10] also showed that odor intensity and familiarity were the discriminating characteristics, whereas cold/warm, and painfulness were not discriminating. Their random forest classifier trained on the individual perceptual ratings of the odors was able to separate patients and controls with a median AUC-ROC of 73.6% (95% CI: 52.8–90.3%), observed during 1000 cross-validation runs.

In this study, the perceptual ratings were used to calculate individual OPF, which distinguished patients and controls with 80% accuracy. This confirmed previous results by Drnovsek et al.[9] that the OPF changes when olfactory function declines. When comparing these two studies, one must keep in mind that, only patients with COVID-related OD were included in Drnovsek et al.,[9] whereas this study included patients with different causes of OD. Although one might expect differences in olfactory perception among OD with a sudden onset (e.g., postviral) and OD with gradual onset (e.g., idiopathic), exploratory analysis showed that OPFs seem to change in the same manner regardless of the cause of OD. Of note, only patients with postviral and idiopathic OD were included in this analysis, as the

sample sizes of other groups were less than five. Another difference is that in Drnovsek et al. participants had to be <45 years old, therefore their age did not contribute much to the change in their olfactory perception. On the other hand, in this study patients were older than controls with a median age of 57 years, which influenced their olfactory function and perception independently.

In this study, participants were randomized to four different odor sets; therefore, we could investigate if one can use different odorants to derive the OPFs. PERMANOVA showed that the OPFs are indeed odorant independent. However, one needs to have an average rating for each odorant and for each descriptor among healthy people to calculate the OPFs. Of note, all the odor sets included odorants that were designed to be broadly distributed in the perceptual space.[10]

This study confirmed previous results, that OPFs can, to some extent, distinguish patients and controls.[9] Accuracy of the random forest classifier was 80%, which is lower compared with the 86% from a previous study.[9] However, the participants were more heterogenous in the cause of OD, duration of OD, and age, all of which could influence their olfactory perception. Furthermore, people were asked to evaluate the odorants on a discrete scale from 1 to 5, whereas in the previous study, a visual analogue scale from 1 to 100 probably captured more information.

In line with previous results, patients perceived odors as less familiar and less intense compared with controls.[9] Interestingly, other perceptual descriptors pleasant, irritating, cold/warm, and painful were not as important. Although some perceptual ratings for a certain odorant might differ among patients and controls as seen in Lötsch et al.,[10] the overall perception of pleasantness, irritation, cold/warm, and painfulness across multiple odorants is not different.

One limitation of this study was the missing perceptual ratings. A k-nearest neighbor method of imputation was used to estimate the missing individual ratings based on the properties of similar neighboring data points, which was probably a good estimation. Another limitation is that the patients' groups per cause were very small. Therefore, only exploratory analysis of the influence of the cause of the OD on the OPF was performed. Another limitation of studying the OPFs is that olfactory perception is influenced by many factors related to the individual such as age,[22] diseases,[23] and the circumstances in which the experiment is performed,[24,25] although such effects were minimized, with participants performing the measurements in the same room with the same computer-controlled olfactometer and the same examiner.

5 | CONCLUSION

This study showed that the OPFs are indeed odorant independent and confirmed that the OPFs can distinguish patients with OD from controls with 80% accuracy. Patients perceived odors as less familiar, less intense, and less edible than controls, whereas other perceptual descriptors pleasant, irritating, warm/cold, and painful were much less important for the separation of patients and controls.

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CONFLICT OF INTEREST STATEMENT

Since 2021, TH has collaborated on research projects with Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; aspuraclip, Berlin, Germany. He received consultancy fees from Baia Foods, Madrid, Spain; Burghart, Holm, Germany; air-up, Munich, Germany. Other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Code and data are available upon request on: https://doi.org/10.7303/syn53278109.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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