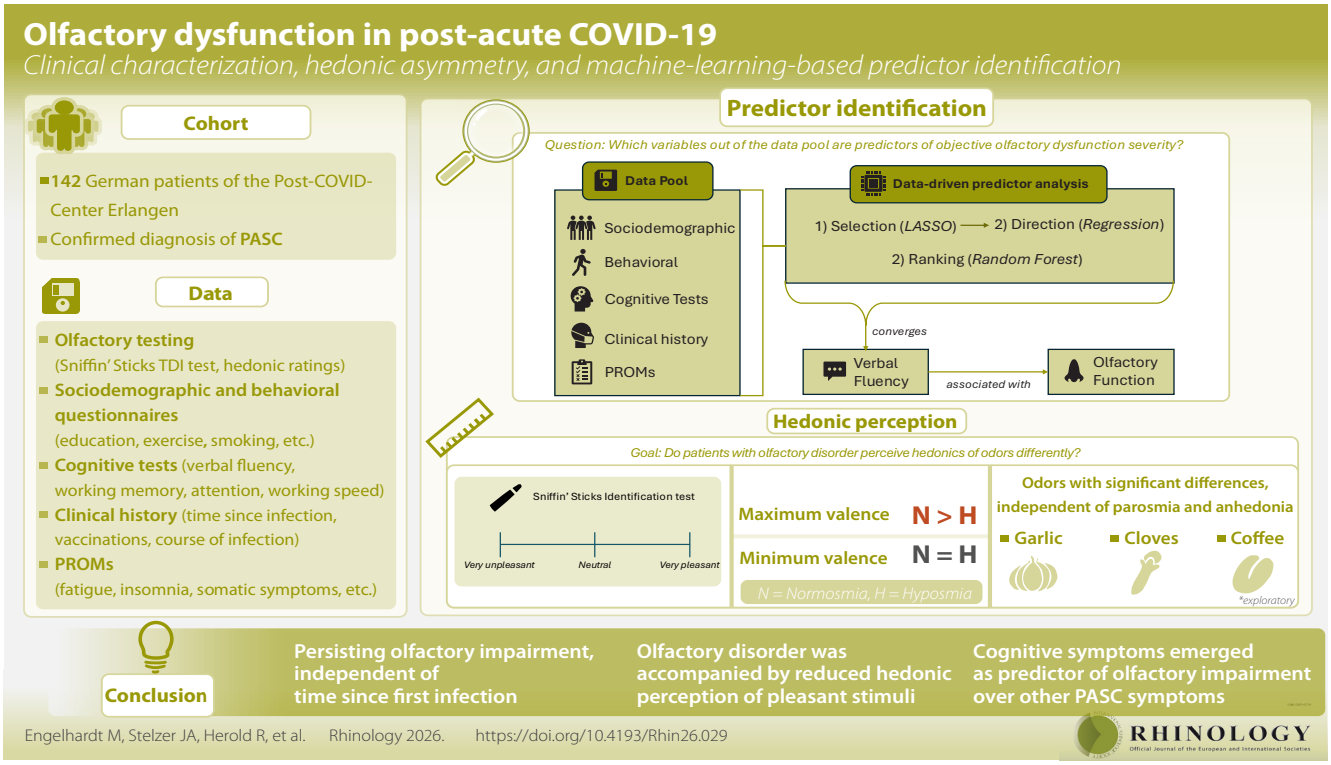
Olfactory dysfunction in post-acute COVID-19: clinical characterization, hedonic asymmetry, and machine-learning-based predictor identification

Moritz Engelhardt[1], Judith A. Stelzer[1], Regina Herold[2], Evelyne Hanc[2], Eva Morawa[2], Yesim Erim[2,3], Jessica Freiherr[1,4]

Rhinology 64: 6, 0 - 0, 2026
https://doi.org/10.4193/Rhin26.029



Abstract

Background: Olfactory dysfunction (OD) is among the most prevalent features of post-acute sequelae of COVID-19 (PASC) and frequently co-occurs with cognitive and neuropsychiatric symptoms. The specific predictors of objective olfactory impairment severity and its relation to systematic shifts in hedonic odor perception remain underexplored. Here, we used data-driven approaches to identify and rank predictors of objective OD severity and examined hedonic valence ratings in patients with and without olfactory impairment. **Methodology**: We examined 144 patients with confirmed PASC diagnoses at 15-63 months post-infection using psychophysical testing (Sniffin' Sticks), standardized cognitive tests for verbal fluency, working memory, attention, and working speed, and patient-reported outcome measures for other symptoms of PASC. Predictors were identified using LASSO regression with voting and random forest variable importance ranking. Hedonic valence ratings from the identification subtest were examined at the group and individual odor level. **Results**: Olfactory function was significantly below normative population values. Verbal fluency emerged as the most robust predictor of olfactory dysfunction severity, converging across both LASSO regression and random forest analyses, and remained significant after controlling for respiratory symptoms. Parosmia, respiratory symptoms, working memory, and somatic symptom burden were also consistently selected. Hyposmic patients showed significantly reduced maximal valence ratings independent of parosmia and anhedonia, while minimal ratings were preserved, with garlic and coffee remaining significant after correction. **Conclusions**: Verbal fluency emerged as the strongest predictor of OD severity in long-term PASC patients. Beyond reduced olfactory sensitivity, hyposmic patients showed asymmetric hedonic impairment, pointing to differential involvement beyond peripheral olfactory loss.

Key words: COVID-19, post-acute COVID-19 syndrome, olfaction disorders, cognition disorders, symptom assessment

Introduction

Following the SARS-CoV-2 pandemic, post-acute sequelae of COVID-19 (PASC) emerged as a major global health burden, affecting approximately 36% of individuals with persistent sensory, cognitive, and physiological impairments [1]. The WHO defines PASC as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation [2]. PASC may manifest heterogeneously across patients: While chemosensory alterations are one of the earliest and most prominent symptoms both during acute and persistent phase [3], symptoms like fatigue, cognitive impairments, insomnia, psychiatric problems, and others are frequently reported [4–6]. Olfactory dysfunction (OD) appears in approximately half of COVID-19 patients [7]. While most patients recover, objective testing reveals persistent olfactory impairment in a significant proportion of patients up to two years post-infection, often exceeding self-reported rates [8]. This comes with a severely detrimental impact on everyday life, like reduced enjoyment of food and social interactions [9,10]. ODs can also come with qualitative alterations, like differently perceived odors (parosmia), or perception of non-existent odors (phantosmia) [11,12]. While smell impairment (hyposmia) or loss (anosmia) seem to rehabilitate with time for many patients, qualitative conditions can stay stable or even worsen over time [13]. Beyond quantitative and qualitative changes, OD can affect hedonic perception. Reductions in the span between the most pleasant and most unpleasant odor perceptions (hedonic range) have been observed in neurodegenerative conditions accompanied by olfactory loss, including Parkinson disease [14] and Alzheimer disease [15]. Emerging evidence suggests that hedonic shifts also occur in PASC, both in patients with and without parosmia [16,17]. Neuropsychological deficits, particularly in memory and executive function, can persist or emerge more than a year after infection [18]. The olfactory system has direct anatomical connections to limbic structures including the hippocampus and amygdala [19], and PASC patients with olfactory complaints show altered functional connectivity in limbic and orbitofrontal networks that also support olfactory processing [20,21], suggesting shared neural substrates for cognitive and olfactory sequelae in PASC. Consistent with this, olfactory impairment is a robust predictor of cognitive decline at the population level [22], and in PASC specifically, the co-occurrence of olfactory and cognitive symptoms is well-established [23,24]. A substantial body of cross-sectional and meta-analytic work on PASC has characterized the prevalence, risk factors, and clinical correlates of OD [25,26]. While associations between cognitive performance and OD have been reported in PASC cohorts, including studies with comprehensive neuropsychological assessments [18,21,27] and machine learning approaches for olfactory classification [28], these investigations have primarily examined olfaction as a predictor or correlate of cognitive outcomes. The present study takes a complementary approach, treating continuous, standardized olfactory function as the primary outcome and using data-driven feature selection to identify cognitive and neuropsychiatric predictors of OD severity in a diagnosed PASC cohort. We assessed a cross-sectional cohort of clinically diagnosed PASC patients recruited from the specialized Post-COVID Center Erlangen (PCCE) using psychophysical olfactory testing (Sniffin' Sticks) on patients 15 to 63 months post-infection, capturing a chronic and stabilized phase of OD. The aims of this study were, first, to characterize the prevalence and severity of OD and related chemosensory symptoms; second, to identify symptom-based predictors of OD severity using LASSO regression and random forest as complementary data-driven approaches; and third, to examine hedonic odor perception across olfactory function groups and individual odor items, given emerging evidence that OD may alter hedonic processing beyond simple detection loss.

Materials and methods

Patient recruitment and testing routine

Patients attending the PCCE between March 2024 and July 2025 were screened for this study. Patients were forwarded from a general practitioner and underwent a standard multidisciplinary diagnostic routine (Figure S1) [6,29]. This included comprehensive cognitive assessments, psychosomatic, internal immunological-rheumatological, ophthalmological, and serological examination, and an extensive battery of patient-reported outcome measures (PROMs) assessing fatigue, sleep, and psychological health (see Supplemental Methods). Patients with acute temporary smell loss or concurrent acute respiratory infections were excluded. Sinonasal comorbidities were recorded in questionnaires. Additionally, participants who reported excessive transient fatigue from previous testing were excluded from further assessment to ensure data quality. Out of 543 screened patients, 178 volunteered. Following exclusions for incomplete data or inconclusive diagnoses, 144 patients (99 female, median age 50.50 [41.75-58.00] years) were included in the final analysis (Table 1).

Olfactory assessment

Olfactory testing was conducted in between examinations or after completion of the testing routine. Participants rated their subjective olfactory abilities retrospectively before their SARS-CoV-2 infection (baseline), at the worst point during their infection (acute), and current on a scale from 0 (complete loss) to 10 (excellent sense of smell and taste). Because patients frequently experience overlap between smell and taste disturbances, participants were instructed to consider these symptoms jointly for this subjective assessment. Quantitative (hyposmia, anosmia) and qualitative (parosmia, phantosmia) ODs were assessed via separate questionnaire items. To facilitate domain differentiation, participants were provided with brief explanations and

Table 1. Demographic and clinical characteristics of the study cohort.

Parameter	Descriptives	Range	Categorized (n)	Total (n)	Statistic	P
Sex			Female (99) / Male (45)	144	W = 2229	.997
Age (years)	50.50 [41.75-58.00]	21-75		144	ρ = .004	.962
Education			Lower secondary school (31) / Intermediate secondary school certificate (43) / University entrance qualification (29) / University degree (BA/MA/Diploma) (39) / Doctorate (PhD) (2)	144	H = 5.21	.266
Time since infection (months)	31.00 [25.00-37.75]	15-63		134	ρ = -.07	.426
Course of acute disease			Non-hospitalized [asymptomatic (6), home (96)] / Hospitalized [hospital (9), intensive care unit (2)]	113	W = 708	.156
Vaccination frequency			0 (5) / 1 (4) / 2 (29) / 3 (76) / 4 (13) / 5 (7)	134	H = 3.73	.589
BMI (kg/m^2)	26.03 [23.29-29.07]	16.92-61.71	Underweight (4) / Normal (52) / Overweight (50) / Obese (27)	133	ρ = -.16	.072
Smoking			Never (96) / Former (29) / Occasional (4) / Daily (<5h) (5) / Daily (>5h) (2)	136	H = 4.77	.312
Alcohol			Never (55) / Once per month or less (32) / 2-4 times per months (33) / 2-3 times per week (7), 4 times per week or more often (6)	133	H = 4.92	.296
Sports			Never (59) / Once per week (38)/ 2-3 times per week (27) / 4-5 times per week (6) / more than 5 times per week (3)	133	H = 3.28	.512
Diabetes			No (135), Yes (9)	144	W = 722	.347
Hypertension			No (132), Yes (12)	144	W = 661	.346
Supplements			No (93), Yes (51)	144	W = 2716.5	.150
Corticosteroids			No (138), Yes (6)	144	W = 213 r = .17 (no: 23.13, yes: 53.97)	.045
Olfactory-relevant comorbidities						
Sinonasal history (CRS/nasal polyps)			No (119), Yes (25) [nasal polyps: 22, CRS: 3]	144	W = 1458	.878
Asthma			No (129), Yes (15)	144	W = 748	.152
Concussion			No (127), Yes (17)	144	W = 1447 r = .19 (no: 25.40, yes: 10.00)	.023
Chemotherapy			No (141), Yes (3)	144	W = 195.5	.828
Zinc deficiency			No (142), Yes (2)	144	W = 191	.401

Discrete variables: absolute counts with group comparison of TDI-PR (Kruskal-Wallis test: H; Wilcoxon rank-sum test: W; P). P values are unadjusted; these bivariate associations are descriptive, and multiplicity is addressed in the LASSO and random forest analyses. Effect sizes: r = Z/√N for significant binary comparisons, reported as absolute magnitudes (group medians in parentheses). Continuous variables: median (IQR) and observed range with Spearman correlation with TDI-PR (ρ, P). Abbreviations: CRS: chronic rhinosinusitis. TDI-PR: Sniffin' Sticks test score as age- and sex-corrected percentile.

examples (e.g., 'I do not perceive any odors') rather than relying solely on medical terminology. Olfactory function was measured using the standardized Threshold-Discrimination-Identification Sniffin' Sticks (TDI) test [30], with scores transformed into age- and sex-corrected percentile ranks (TDI-PR) based on normative data [31,32]. During the identification subtest, patients additionally rated valence (-5 to 5) and intensity (0 to 10).

Statistical analysis

Statistical analyses were conducted with R (version 4.3.1) (33). Group comparisons utilized the Wilcoxon rank-sum or Kruskal-Wallis tests with Bonferroni-Holm-corrected Dunn's post-hoc tests where applicable (34). To handle missing data across multiple domains, multiple imputation (20 datasets) was performed prior to predictive modeling. We applied LASSO regression with

Table 2. Symptoms of PASC and their association with olfactory function (TDI-PR).

Parameter	Scale	Descriptives	n	Below norm, n (%)	Statistic	P
Olfaction			144			
Olfactory function (TDI)	0 – 48	31.0 [27.3-34.0]	144	Hyposmic: 58 (40.3), Anosmic: 6 (4.2)		
T	1 – 16	7.30 [5.53 – 9.00]	144			
D	0 – 16	12 [10 - 13]	144			
I	0 – 16	12 [11 - 14]	144			
Olfactory function (TDI percentile rank)	0 – 100	23.80 [9.88 - 45.45]	144			
Self-assessment (olfactory disorder)			144	Hyposmic: 54 (37.5), Anosmic: 8 (5.6)		
Self-assessment (VAS, current)	0-10	7 [5-9]	144	Decrease: 80 (55.6), Same: 58 (40.3), Increase: 6 (4.2)	$\rho = .38$	< .001
Self-assessment (VAS, acute)	0-10	3 [0 - 7]	144		$\rho = .27$	.001
Self-assessment (VAS, baseline)	0-10	9 [8-10]	144		$\rho = -.003$	.968
Qualitative dysfunction (any)			144	46 (31.9)	W = 2795.5, r = .19	.020
Parosmia			144	36 (25)	W = 2611.5, r = .26	.002
Phantosmia				19 (13.2)	W = 1076.5	.514
Cognition						
Verbal fluency (RWT as percentile rank)	0 – 100	22 [9-48]	138	58 (42)	$\rho = .18$	.036
Working memory (DSB, percentile rank)	0 – 100	34 [12-73]	137	49 (35.8)	$\rho = .22$	.011
Attention (D2 KL, percentile rank)	0 – 100	21 [7-46]	134	57 (42.5)	$\rho = .12$	.155
Working speed (D2 BZO, percentile rank)	0 – 100	16 [4-42]	134	68 (50.7)	$\rho = .07$	.402
Self-reported symptom measures						
Fatigue (FSS)	63 – 9	58 [52-61]	134	126 (94)	$\rho = -.12$	.183
Insomnia (ISI)	28 – 0	14 [7.25-19]	133	66 (49.6)	$\rho = -.20$	.023
Somatic symptom disorder (SSD)	48 – 0	25 [15-34]	133	88 (66.2)	$\rho = -.11$	.193
Depression (PHQ-9)	27 – 0	10 [7-15]	134	81 (60.4)	$\rho = -.11$	.222
Somatic symptom burden (PHQ-15)	30 – 0	11 [6-14]	134	95 (70.9)	$\rho = -.24$	.005
Anxiety (GAD-7)	21 – 0	6 [2-11]	134	42 (31.3)	$\rho = -.07$	.428
Post-Covid-Score (Bahmer et al.)						
Total score	59 – 0	42.0 [33.0-50.5]	133	No/Mild: 1 (0.7), Moderate: 17 (11.8), Severe: 115 (79.9)	$\rho = -.32$	< .001
Chemosensory deficits			133	No (75), Yes (58)	W = 3225.5, r = -.41	< .001
Fatigue			133	No (4), Yes (129)	W = 343.5	.263
Exercise intolerance			133	No (5), Yes (128)	W = 612.5	< .001
Joint or muscle pain			133	No (27), Yes (106)	W = 1817.5	.031
ENT ailments			133	No (52), Yes (81)	W = 2617.5	.018
Respiratory symptoms			134	No (60), Yes (74)	W = 2814.0	.008
Chest pain			134	No (57), Yes (77)	W = 2355.0	.471
Gastrointestinal ailments			134	No (66), Yes (68)	W = 2761.0	.022
Neurological ailments			134	No (11), Yes (123)	W = 753.5	.535
Dermatological ailments			134	No (64), Yes (70)	W = 2039.0	.372
Infection signs			134	No (82), Yes (52)	W = 2469.5	.124
Sleep disturbance			133	No (24), Yes (109)	W = 1528.0	.199

Continuous variables: median (IQR). Correlations: Spearman ρ with TDI-PR. Group comparisons: Wilcoxon rank-sum test. P values are unadjusted; these bivariate associations are descriptive, and multiplicity is addressed in the LASSO and random forest analyses. Effect sizes: $r = Z/\sqrt{N}$, reported as absolute magnitudes. Clinical cutoffs: PHQ-9 ≥ 10; GAD-7 ≥ 10; ISI ≥ 15; PHQ-15 ≥ 10; FSS ≥ 36; cognitive percentile rank < 16; SSD-12 ≥ 23; Hyposmia: TDI ≤ 30.5; Anosmia: TDI ≤ 16. Abbreviations: FSS: Fatigue Severity Scale; ISI: Insomnia Severity Index; SSD: Somatic Symptom Disorder – B Criteria Scale, 12 items; PHQ-9: Patient Health Questionnaire - 9 items; PHQ-15: Patient Health Questionnaire – 15 items; GAD-7: Generalized Anxiety Disorder scale – 7 items; RWT: Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward) from the

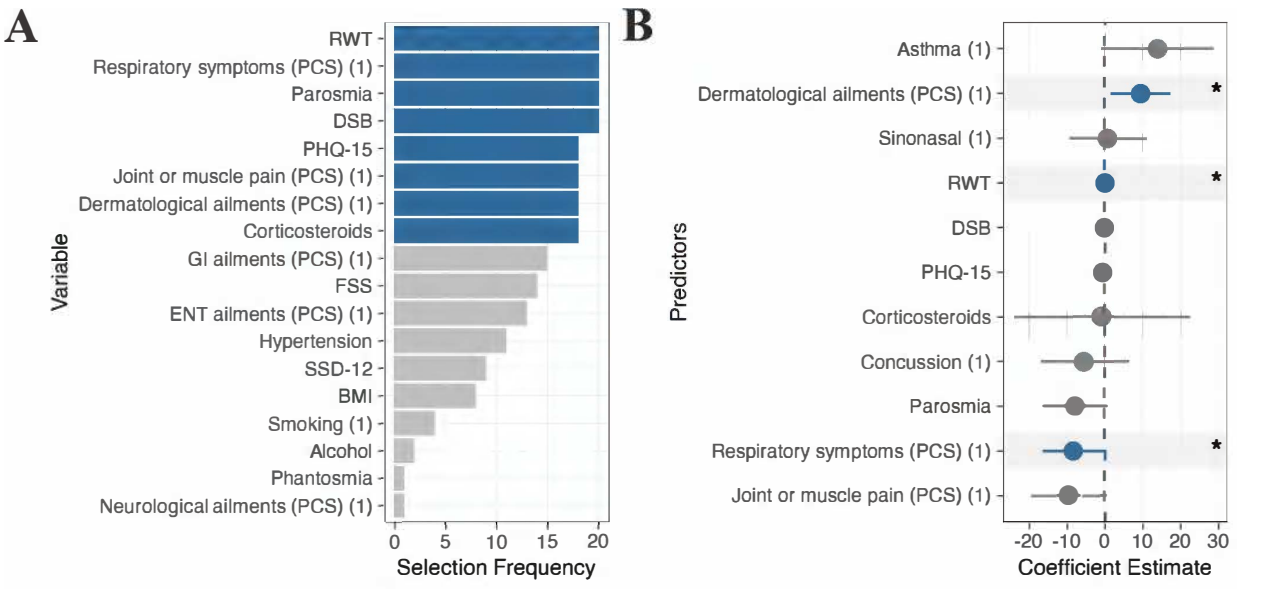


Figure 1. Results from LASSO feature selection and linear regression model with TDI-PR as target variable. (A) Ranked frequency of predictors after LASSO feature selection on 20 MICE imputed datasets. Parameters that crossed the threshold of selection in 18/20 datasets (90%) are marked in blue. (B) Forest plot showing the coefficient estimates of final model with olfactory function as percentile rank as dependent variable, the features selected in LASSO as predictors, and relevant comorbidities as covariates. Error bars indicate the 95% CI. Significant effects are marked blue with significance labels (*** P < .001; ** P < .01; * P < .05). Parentheses after bivariate values represent the effect for the binary value. Abbreviations: TDI-PR: olfactory function as Sniffin' Sticks test score standardized on age- and sex-corrected normative data; PCS: Post-COVID syndrome score; RWT: Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward) from the Wechsler Memory Scale-Revised; FSS: Fatigue Severity Scale; PHQ-15: Patient Health Questionnaire - 15 items, SSD: Somatic Symptom Disorder - B Criteria Scale, 12 items.

10-fold cross-validation to identify robust predictors of olfactory function, alongside a random forest model to assess complex non-linear variable importance. Pre-existing conditions known to affect olfaction (e.g., sinonasal disease, asthma, concussion) were included as forced covariates (Table S1). To analyze hedonic perception, we restricted the dataset to trials where odor intensity was perceived as ≥ 2. Linear models and Linear Mixed Models (LMMs) with random intercepts for participants were utilized to evaluate hedonic ranges and odor-level valence effects across dysfunction groups, adjusting for age, sex, time since infection (TSI), parosmia, anhedonia, and trial-level intensity. Anhedonia (PHQ-9 item 1) was included as a covariate given its documented association with sensory hedonic perception [14]. Detailed descriptions of imputation parameters, variable selection criteria, bootstrapping methods, and R packages are available in Supplemental Methods. Significance was set at P < 0.05.

Results

Characterization of olfactory function

Olfactory function was assessed with objective TDI testing and subjective self-assessment (Table 2) and compared across clinical and demographic variables (Table 1). TSI ranged from 15 to 63 months but was not significantly associated with changes in TDI-PR (ρ = - 0.07; P = .43). Median TDI-PR was numerically higher in patients with outpatient treatment during acute phase (Median: 24) compared to hospitalized patients (Median: 16), but the difference was not significant (W = 708; P = .16). Overall, 64 patients (44.4%) showed test scores indicating OD. TDI-PR was significantly below the expected population average of 50 (W = 1385; P < .001; r = 0.64). Subjectively perceived OD was noted by 62 (43.1%) patients. While self-assessed and TDI-derived OD overlapped in only 88 (61.1%) of patients, higher self-assessments using visual analog scales showed a moderate positive correlation with higher TDI scores (ρ = 0.38; P < .001). The correlation was mainly driven by patients who rated their

Wechsler Memory Scale-Revised (WMS-R); d2: d2. Test of Attention; *Legend Table 2 continued.*

KL = concentration performance (Konzentrationsleistung); BZO = processed target objects (Bearbeitete Zielobjekte). TDI-PR: Sniffin' Sticks test result as age- and sex-corrected percentiles; T: threshold; D: discrimination; I: identification. Scale ranges are given as worst - best. PASC: post-acute sequelae of COVID-19; TDI-PR: Sniffin' Sticks test score as age- and sex-corrected percentile.

Table 3. Pooled linear regression results with TDI-PR as dependent variable, LASSO selected variables as predictors, and comorbidities as forced covariates.

Predictor	B	SE	β	t	df	P
Dermatological ailments (PCS)	9.48	4.00	0.40	2.37	116.23	.019
RWT	0.16	0.08	0.18	2.09	127.36	.039
Respiratory symptoms (PCS)	-8.41	4.09	-0.35	-2.06	118.80	.042
Asthma	13.92	7.53	0.59	1.85	126.02	.067
Joint or muscle pain (PCS)	-9.43	5.15	-0.40	-1.83	96.59	.070
Parosmia	-7.70	4.41	-0.32	-1.75	128.53	.083
PHQ-15	-0.46	0.40	-0.11	-1.15	111.31	.252
DSB	0.06	0.06	0.09	1.02	125.35	.309
Concussion	-5.30	5.95	-0.22	-0.89	126.72	.375
Sinonasal	0.83	5.24	0.03	0.16	128.75	.875
Corticosteroids	-0.80	11.84	-0.03	-0.07	128.29	.946

Abbreviations: TDI-PR: olfactory function as Sniffin' Sticks test score standardized on age- and sex-corrected normative data; PCS: Post-COVID syndrome score; RWT: Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward) from the Wechsler Memory Scale-Revised (WMS-R); PHQ-15: Patient Health Questionnaire - 15 items. B: unstandardized coefficient; SE: standard error; β: standardized coefficient (all predictors standardized, including binary); t: test statistic. Estimates were pooled across m = 20 multiply imputed datasets using Rubin's rules; df are Barnard-Rubin degrees of freedom and are therefore non-integer. Binary predictors coded no = 0, yes = 1; asthma, concussion, sinonasal history and corticosteroid use were entered as forced covariates. RWT and DSB are percentile ranks. n = 144. P values are unadjusted.

olfactory function as 5 or lower ($\rho = 0.57$; $P < .001$). More than half of patients (80; 55.6%) reported decreased olfactory function compared to baseline, with retrospective self-assessment differing significantly across timepoints ($H(2) = 132.6$; $P < .001$; $\varepsilon^2 = 0.30$). Current qualitative OD (parosmia, phantosmia) was self-reported by 46 (31.9%) patients. TDI-PR was significantly lower in patients with compared to without parosmia ($W = 2611.5$; $P = .002$; $r = 0.26$).

Evaluation of predictor effects via linear regression and random forest

Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test; RWT), digit span backwards (DSB) test from the Wechsler Memory Scale-Revised for working memory, subjective parosmia, Patient-Health-Questionnaire - 15 items (PHQ-15) for burden of somatic symptoms, corticosteroid intake, and Post-Covid Syndrome score (PCS) subitems for dermatological ailments, respiratory symptoms, and joint/muscle pain were consistently selected during LASSO variable selection (Figure 1A). Three predictors were significant in the final model: RWT test ($B = 0.16$; $SE = 0.08$; $t(127.4) = 2.09$; $P = .039$), respiratory symptoms ($B = -8.41$; $SE = 4.09$; $t(118.8) = -2.06$; $P = .042$), and dermatological ailments ($B = 9.48$; $SE = 4.0$; $t(116.23) = 2.37$; $P = .019$) (Figure 1B; Table 3). The inclusion of sinonasal comorbidities, asthma, and past concussion as forced covariates did not substantially alter estimates or significance levels for most predictors. Only corticosteroid intake was unstable across specifications due to near-complete confounding with asthma diagnosis but was non-significant in both models (Table S2). In the random forest model, RWT test scores showed the highest importance (%IncMSE = 6.92), followed by DSB test scores (%IncMSE = 4.04), and dermatological ailments (%IncMSE = 3.87) (Figure 2; Figure S2). Since respiratory symptoms were selected as important predictors of TDI-PR alongside cognitive performance, we evaluated whether these associations were independent using partial correlation analysis. The association between TDI-PR and both DSB (partial Spearman $\rho = 0.20$; $P = .024$) and RWT (partial Spearman $\rho = 0.24$; $P = .006$) remained significant while controlling for respiratory symptoms. To examine whether associations between TDI-PR and cognitive performance were driven by specific TDI subtests, correlations with threshold, discrimination, and identification tests were computed separately. Correlations with individual subtests were weaker than with the composite score, and identification showed the weakest association for both cognitive measures (Table S3).

Asymmetric hedonic impairment in hyposmic patients

Hedonic range was found to be lower in hyposmic (EMM: 7.59) compared to normosmic (EMM: 8.05) patients, however the difference was not significant ($t(115) = -1.37$; $P = .17$; $d = -0.27$; Table S4). Comparing only the maximal perceived valence ratings, hyposmic patients showed significantly reduced values compared to normosmic (EMM: 3.67 vs. 4.18; $t(115) = -2.37$; $P = .019$; $d = -0.47$) (Figure 3A). No such difference was observed for

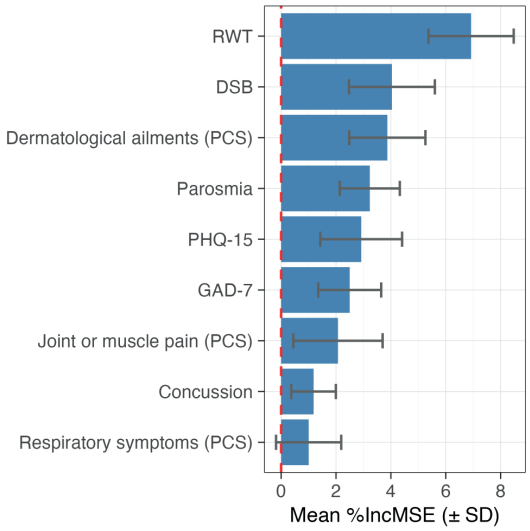


Figure 2. Results from the random forest model, with TDI-PR as target variable. Feature ranking after highest mean importance (%IncMSE) with error bars showing standard deviation (SD) across 20 imputed datasets. Only predictors with Mean %IncMSE > 1 are displayed. Standard deviation (SD) across 20 imputed datasets. Abbreviations: TDI-PR: olfactory function as Sniffin' Sticks test score standardized on age- and sex-corrected normative data; RWT: Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward) from the Wechsler Memory Scale-Revised; PCS: Post-COVID syndrome score; GAD-7: Generalized Anxiety Disorder scale - 7 items; %IncMSE: percentage increase in mean squared error.

the lowest perceived valence ratings (EMM: -3.92 vs. -3.87; t(115) = -0.22; P = .82; d = -0.04) (Figure 3B). Male patients showed significantly lower maximum valence ratings (EMM: 3.52 vs. 4.33; t(115) = -3.57; P < .001; d = -0.74; Table S5) and hedonic range (EMM: 7.24 vs. 8.40; t(115) = -3.31; P < .001; d = -0.68) compared to female patients. In a supplemental continuous analysis using TDI-PR rather than clinical OD groups, maximal valence (B = 0.01; 95% bootstrap CI [0.001, 0.019]; P = .039) showed a weak positive association with TDI-PR, whereas minimal valence did not (B = 0.003; 95% bootstrap CI [-0.006, 0.013]; P = .48), mirroring the asymmetry observed at the group level (Table S4). In an exploratory per-odor analysis (OD×odor interaction P = .06), hyposmic patients rated the valence of garlic (Δ = -1.35; SE = 0.45; t(1125.7) = -3.00; P(uncorrected)= .003; P(Holm)= .04; d = -0.62), cloves (Δ = -1.15; SE = 0.45; t(1144.9) = -2.55; P(uncorrected)= .01; P(Holm)= .16; d = -0.53), and coffee (Δ = -0.90; SE = 0.46; t(1158.3) = -1.96; P(uncorrected)= .05; P(Holm)= .70; d = -0.41) as lower, while only garlic survived multiple comparisons corrections (Figure 3C; Table S6). Consistent with the group-level contrasts, higher TDI-PR was positively associated with higher valence ratings for coffee (P(uncorrected)= .003; P(Holm)= .04), garlic (P(uncorrected)= .006; P(Holm)= .09), cloves (P(uncorrected)= .02; P(Holm)= .25), and leather (P(uncorrected)= .03; P(Holm)= .44), while only coffee survived correction. Taken together, hyposmic patients showed a significantly reduced upper hedonic limit while the lower limit remained intact at the clinical group level. The continuous analysis showed a similar pattern, with TDI-PR significantly predicting only the upper hedonic limit. In per-odor contrasts, garlic, cloves, and coffee showed the largest reductions, with garlic and coffee surviving correction in the group-level and continuous analyses, respectively.

Discussion

In this comprehensively evaluated PASC cohort, complementary data-driven approaches identified verbal fluency as the most robust predictor of TDI-PR. Item-level profiling revealed an asymmetric hedonic impairment in hyposmic patients, driven by a selectively reduced upper bound of valence ratings. Together, these findings integrate the cognitive and perceptual dimensions of OD in PASC, which have previously been examined only in isolation. The cohort showed significantly sub-average TDI-PRs, despite a wide range of TSI up to 63 months, consistent with recent studies describing olfactory impairment persisting up to 3 years post-infection [35]. Retrospective self-assessment confirmed lasting subjective decline, with more than half of the patients reporting a decrease. The frequent discrepancy between subjective self-assessment and objective testing in our cohort aligns with recent literature [26], reinforcing the necessity of routine psychophysical testing in PASC evaluations [36]. Contrary to current literature [37], acute infection severity was not significantly associated with olfactory impairments, potentially reflecting limited statistical power in the severe subgroups.

Verbal fluency emerged as a significant factor in the LASSO regression and as top predictor in the random forest model alongside working memory. Findings of predictive importance of verbal fluency therefore converged in two computational approaches with fundamentally different assumptions. Furthermore, TDI-PR was significantly correlated with both working memory and verbal fluency, even when correcting for respiratory problems. As the PCS score assesses patient-reported symptom complexes rather than specific pathophysiological mechanisms, the respiratory item should be interpreted as reflecting general respiratory symptom burden rather than a specific pulmonary process. Together, these findings highlight verbal fluency and working memory as robust predictors of olfactory impairments in PASC, an association that persists at 15 to 63 months post-infection. Importantly, the cognitive-olfactory associations were not primarily driven by methodological confounds. Suprathreshold olfactory tests such as discrimination and identification are known to involve semantic memory and executive function, while threshold is considered a primarily sensory measure [38]. In our data, verbal fluency was most strongly associated with threshold, and both cognitive measures showed their weakest

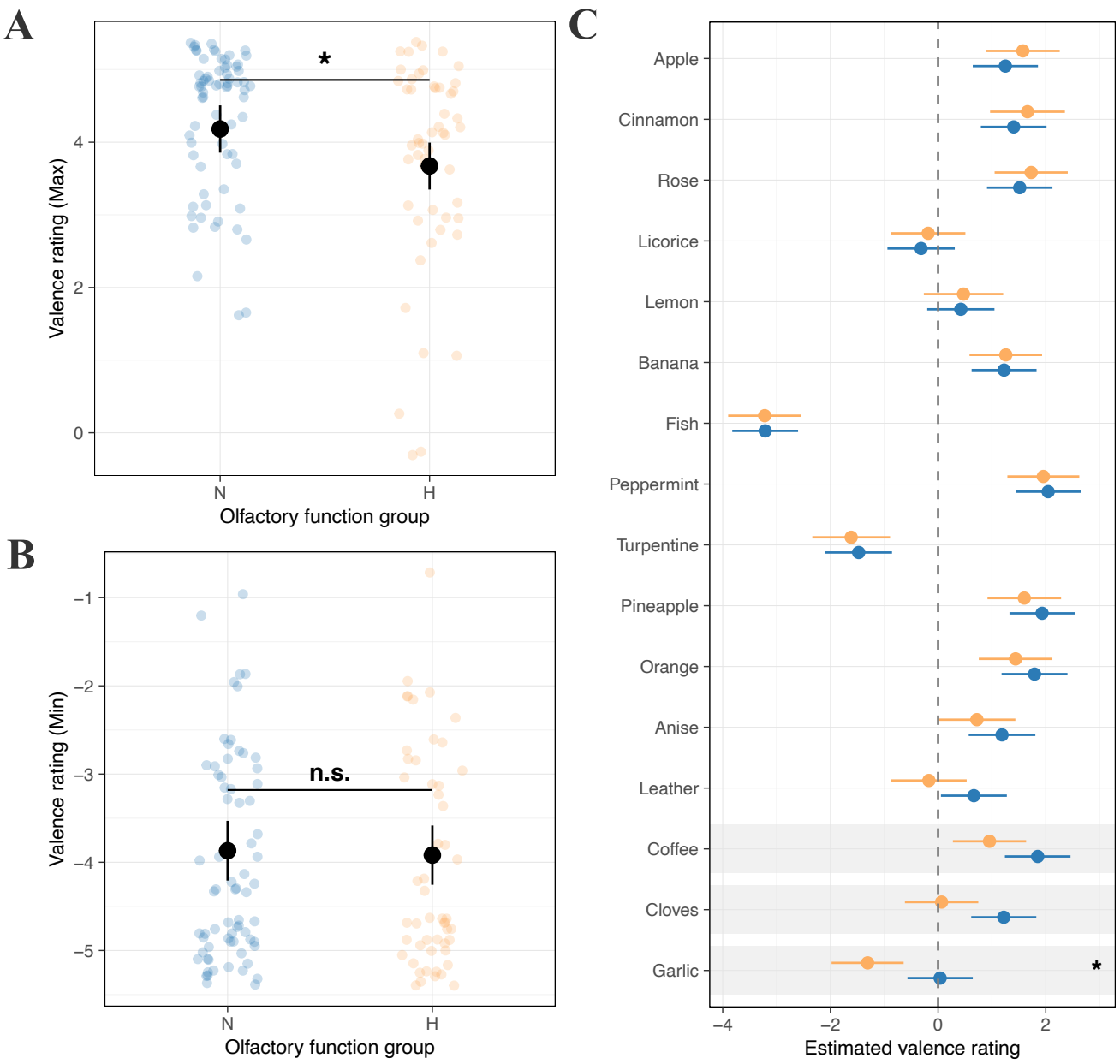


Figure 3. Hedonic odor perception compared between normosmic (blue) and hyposmic (orange) patients. (A) Maximum and (B) minimum perceived valence per patient; coloured points show individual patients, black points and bars show estimated marginal means with 95% confidence intervals from linear models adjusted for age, sex, time since infection, parosmia, and anhedonia. (C) Estimated valence ratings per odor item from the linear mixed model, additionally adjusted for trial-level intensity, with odors ordered by the magnitude of the hyposmic–normosmic difference. Group differences in (A) and (B) are indicated by bars above the groups. In (C), asterisks denote Bonferroni-Holm-corrected significance across the 16 odors, and shaded rows denote odors significant before correction; uncorrected and corrected values are reported in Table S6. Anosmic patients were excluded due to insufficient sample size for stable estimates. Analysis restricted to trials with intensity ratings ≥ 2 to ensure meaningful hedonic evaluation (*** P < .001; ** P < .01; * P < .05; n.s. = not significant).

association with identification, suggesting the link extends beyond shared cognitive task demands. While some domains like cognition were represented by multiple variables, the applied modeling approaches evaluate predictors individually, and multicollinearity diagnostics did not indicate problematic redundancy among predictors. Verbal fluency has been identified as the cognitive domain most consistently affected in PASC before [23,36]. Our findings extend this by demonstrating that verbal fluency performance is also the strongest cognitive predictor of TDI-PR. Inconsistent cognitive-olfactory associations in PASC literature [39,40] often reflect methodological variations. Studies using domain-specific cognitive tests and objective olfaction

detect associations more reliably than those using screening instruments or self-reports [36]. By employing domain-specific tests and regularized variable selection, which together account for symptom collinearity beyond the capacity of standard bivariate approaches, we demonstrate that verbal fluency is a robust predictor. Our findings are rooted in the neural basis of olfactory and cognitive processing. Olfactory processing areas are directly connected with fronto-temporal regions involved in verbal fluency, including the orbitofrontal cortex and temporal lobes [19]. These regions exhibit the most consistent structural and functional disruptions in PASC patients [41–43], consistent with longitudinal evidence of SARS-CoV-2-induced changes specifically in olfactory and limbic regions [44]. Furthermore, altered thalamic connectivity within the olfactory network has been found to correlate negatively with cognitive tests for short term verbal memory, possibly indicating compensatory mechanisms at the neural level [45]. Our findings provide behavioral evidence consistent with this shared neural vulnerability.

Beyond cognitive predictors, several somatic symptom domains were selected by LASSO or ranked highly in the random forest model, including burden of somatic symptoms (PHQ-15) and the PCS score items dermatological ailment, respiratory symptoms, and joint/muscle pain. The broader emergence of somatic symptom domains as predictors alongside cognitive variables points to the multisystemic nature of OD in PASC, in which olfactory outcomes are shaped by both central neurological and peripheral somatic processes. For other health and sociodemographic factors, no influence on olfactory symptoms was found. This is consistent with imaging studies that similarly did not find associations between these factors and changes in olfactory brain regions [43,44].

We observed one-sided compression of valence perception in hyposmic PASC patients, while hedonic range did not differ significantly between groups. This differs from observations in Parkinson patients, where two-sided compression was observed in hyposmic patients [14], and more closely mirrors hedonic alterations found in Alzheimer patients, where maximal valence was found to be reduced, while the lower bound remained intact [15]. Previous studies on PASC using the Sniffin' Sticks Parosmia Test (SSParoT) [46] found reduced hedonic range in patients both with and without parosmia [16,17], a more pronounced pattern than the asymmetric upper-bound compression observed in our cohort. Our findings are consistent with fMRI evidence that hedonic processing of pleasant and unpleasant odors engages partially dissociable limbic circuits [47], which may be differentially vulnerable to post-viral damage. Notably, the preserved lower hedonic limit may in part reflect a floor effect, as highly unpleasant odors leave limited potential for further hedonic reduction. Lower maximum valence perception in male patients was consistent with established sex differences in hedonic odor perception. At odor level, garlic, cloves, and coffee showed the largest reduction in valence in hyposmic patients, while only garlic in group-level and coffee in continuous analysis remained significant after correction for multiple comparisons across 16 odor items. These odors resemble chemically complex, food related compounds that overlap with the most commonly reported parosmia triggers [48], yet the effect persisted after adjusting for parosmia. Notably, these effects also persisted after adjusting for general anhedonia. If replicated, greater hedonic impairment for chemically complex odors rather than uniform attenuation, would argue against a purely affective explanation and would be consistent with differential vulnerability of olfactory processing pathways. The broader pattern of odor-specific vulnerability requires targeted replication.

The study was limited due to its observational nature, its integration into existing testing practice, and time constraints for the olfactory testing. As the olfactory testing was not advertised beforehand, patients tested for this study originally attended the PCCE for symptoms unrelated to their olfactory function. The voluntary nature of participation and the integration into clinical routine may introduce selection bias, potentially excluding patients with isolated OD or severe fatigue. Sinonasal comorbidities were self-reported rather than endoscopically verified, as no otorhinolaryngologist was involved. Subclinical sinonasal pathology could therefore influence olfactory function independently of PASC. However, we controlled for this statistically to maintain clinical representativeness. Although no matched control group was available, the usage of age- and sex-corrected normative percentile ranks provided population-level comparisons. The cross-sectional design did not permit causal conclusions and longitudinal perspectives, and the retrospective self-assessment of pre-infection and acute-phase olfactory function was subject to recall bias. Qualitative OD was assessed with self-reported olfactory function rather than a test like the SSParoT, which might have underestimated parosmia prevalence [46], but adding another test would not have been possible due to time constraints and out of respect for the patients' energy. While the explained variance of the pooled regression model was modest ($R^2 = 0.21$), this is consistent with the heterogeneity of a clinical PASC cohort where unmeasured factors, including viral variant, genetic susceptibility, and treatment history, likely contribute substantially to olfactory outcomes.

Longitudinal follow-up of clinically well-defined PASC cohorts would clarify whether the olfactory-cognitive association reflects a shared static deficit or a progressive trajectory. The finding that verbal fluency is the strongest cognitive predictor of OD is particularly noteworthy given evidence that olfactory training may yield benefits specifically in verbal fluency and ver-

bal memory [49], suggesting a potential bidirectional therapeutic pathway that encourages further investigation. The relationship between hedonic perception and neuropsychiatric symptom burden, including depressive and somatic symptoms, should be investigated further. Future studies incorporating specific inflammatory and neural injury markers, such as cytokines or neurofilament light chain, could clarify whether neuroinflammation mediates the observed olfactory-cognitive association. Lastly, neuroimaging studies in long-term PASC patients could explain whether the behavioral associations observed here correspond to structural or functional alterations in shared olfactory-cognitive circuits.

Conclusion

Verbal fluency is a robust predictor of OD severity in PASC 15-63 months post-infection. Beyond reduced olfactory sensitivity, hyposmic individuals showed asymmetric hedonic impairment of the upper hedonic limit, a pattern not fully explained by parosmia status or anhedonia, suggesting that central processing may be differentially affected. Taken together, the association between cognitive performance and OD severity, and the compression of the upper hedonic limit among hyposmic patients, suggest that PASC olfactory impairment is not limited to peripheral sensory loss but involves higher-order dimensions of odor processing, including cognitive evaluation and affective appraisal. These findings underscore the clinical overlaps of olfactory and cognitive sequelae in PASC and support the integration of domain-specific cognitive assessment into the clinical evaluation of persistent OD.

Abbreviations

d2: d2 Test of Attention;
KL = concentration performance (Konzentrationsleistung);
BZO = processed target objects (Bearbeitete Zielobjekte); DSB: working memory test (Digit Span Backward) from the Wechsler Memory Scale-Revised; EMM: Estimated marginal means; FSS: Fatigue Severity Scale; GAD-7: Generalized Anxiety Disorder scale - 7 items; ISI: Insomnia Severity Index; LASSO: Least Absolute Shrinkage and Selection Operator; OD: Olfactory Dysfunction; PASC: Post-acute Sequelae of COVID-19; PCCE: Post-Covid-Center Erlangen; PCS score: Post-Covid Syndrome score; PHQ-9: Patient Health Questionnaire - 9 items; PHQ-15: Patient Health Questionnaire – 15 items; PR: Percentile rank; RWT: Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test); SSD: Somatic Symptom Disorder – B Criteria Scale, 12 items; SSParoT: Sniffin' Sticks Parosmia Test; TDI: Threshold-Discrimination-Identification score from the Sniffin' Sticks test; TDI-PR: Sniffin' Sticks test score as age- and gender-corrected percentile; TSI: Time since infection; %IncMSE: percentage increase in mean squared error.

Acknowledgments

We want to thank the patients that agreed to participate in this study. We furthermore want to thank the physicians, scientists, and students of the affiliated research groups and the Post-COVID-Center Erlangen that were involved in patient recruitment, organization, or data collection, especially Dr. Brigitte Greiner, Tim Diener, and Dr. Johannes Krehbiehl. Moritz Engelhardt wants to thank Cusanuswerk e.V. for supporting the project with a doctoral scholarship. The present work was performed in (partial) fulfilment of the requirements for obtaining the degree „Dr. rer. biol. hum." from Friedrich-Alexander-Universität Erlangen-Nürnberg for Moritz Engelhardt.

Author contributions

JF, YE, EM, ME conceptualized the idea. ME and JF designed the study. ME collected, analyzed and interpreted the data with close supervision by JF. JS supported in patient testing. RE and EH supported with data preparation. ME drafted and wrote the manuscript. JF, YE, and EM critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no competing interests.

Funding

The study is funded by the Psychiatric and Psychotherapeutic Clinic of University Hospital Erlangen, Germany. ME received a scholarship of Cusanuswerk e.V. for this.

References

1. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global prevalence of Long COVID, its subtypes and risk factors: an updated systematic review and meta-analysis. Open Forum Infect Dis. 2025;12(9):ofaf533.
2. World Health Organization. Post COVID-19 condition (Long COVID) [Internet]. Copenhagen: WHO Regional Office for Europe; 2022 [cited 2026 Mar 12]. Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition
3. Bianco MR, Ralli M, Minni A, Greco A, de Vincentiis M, Allegra E. Evaluation of olfactory dysfunction persistence after COVID-19: a prospective study. Eur Rev Med Pharmacol Sci. 2022;26(3):1042–8.
4. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133–46.
5. Kluge S, Janssens U, Schälte G, et al. S3-Leitlinie – Empfehlungen zur Therapie von Patienten mit COVID-19. AWMF; 2024. https://register.awmf.org/assets/guidelines/113-001l_S3_Empfehlungen-zur-Therapie-von-Patienten-mit-COVID-19_2026-05.pdf
6. Hanc E, Koller K, Herold R, Erim Y, Morawa E. Cognitive impairment, depression, and fatigue in post-COVID and post-vaccination syndrome: a large-scale cross-sectional study. Eur Arch Psychiatry Clin Neurosci. 2026;276(1):221–34.

7. Saniasiaya J, Islam MA, Abdullah B. Prevalence of olfactory dysfunction in coronavirus disease 2019 (COVID-19): a meta-analysis of 27,492 patients. Laryngoscope. 2021;131(4):865–78.
8. Boscolo-Rizzo P, Hummel T, Spinato G, et al. Olfactory and gustatory function 3 years after mild COVID-19—a cohort psychophysical study. JAMA Otolaryngol Head Neck Surg. 2024;150(1):79–81.
9. Boesveldt S, Postma EM, Boak D, et al. Anosmia—a clinical review. Chem Senses. 2017; 42(7):513-523.
10. Oleszkiewicz A, Croy I, Hummel T. The impact of olfactory loss on quality of life: a 2025 review. Chem Senses. 2025;50:bjaf023.
11. Lechien JR, Vaira LA, Saussez S. Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: a multicentre prospective study. J Intern Med. 2023;293(1):82–90.
12. Kim S, Finlay JB, Ko T, Goldstein BJ. Long-term olfactory loss post-COVID-19: pathobiology and potential therapeutic strategies. World J Otorhinolaryngol Head Neck Surg. 2024;10(2):148–55.
13. Ohla K, Veldhuizen MG, Green T, et al. Increasing incidence of parosmia and phantosmia in patients recovering from COVID-19 smell loss. medRxiv [Preprint]. 2021. Available from: https://doi.org/10.1101/2021.08.28.21262763
14. Utz KS, Martini M, Mrochen A, et al. A multisensory deficit in the perception of pleasantness in Parkinson's disease. J Parkinsons Dis. 2021;11(4):2035–45.
15. Joussain P, Bessy M, Fournel A, et al. Altered affective evaluations of smells in Alzheimer's disease. J Alzheimers Dis. 2016;49(2):433–41.
16. Eland SN, Bais B, Kooper DP. The SSParoT as a test in post-COVID-19 patients with parosmia. J Community Med Public Health. 2023;7:320.
17. Sekine R, Menzel S, Hähner A, Mori E, Hummel T. Assessment of postviral qualitative olfactory dysfunction using the short SSParoT in patients with and without parosmia. Eur Arch Otorhinolaryngol. 2023;280(1):469–72.
18. Voruz P, De Alcântara IJ, Nuber-Champier A, et al. Persistence and emergence of new neuropsychological deficits following SARS-CoV-2 infection: a follow-up assessment of the Geneva COVID-COG cohort. J Glob Health. 2024;14:05008.
19. Soudry Y, Lemogne C, Malinvaud D, Consoli SM, Bonfils P. Olfactory system and emotion: common substrates. Eur Ann Otorhinolaryngol Head Neck Dis. 2011;128(1):18–23.
20. Thomasson M, Voruz P, Cionca A, et al. Markers of limbic system damage following SARS-CoV-2 infection. Brain Commun. 2023;5(4):fcad177.
21. Díez-Cirarda M, Yus M, Gómez-Ruiz N, et al. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. Brain. 2023;146(5):2142–52.
22. Yeo BSY, Song HJJMD, Tan BKJ, et al. Olfactory impairment and incident cognitive decline: a systematic review and meta-analysis. Int Forum Allergy Rhinol. 2025;15(12):1347–58.
23. Azcue N, Del Pino R, Saenz De Argandoña O, et al. Understanding the olfactory role in post-COVID cognitive and neuropsychiatric manifestations. Front Psychol. 2024;15:1407887.
24. Voruz P, Cionca A, de Alcantara IJ, et al. Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome: is anosognosia a key determinant? Brain Commun. 2022;4(2):fcac057.
25. Liu N, Yang D, Zhang T, Sun J, Fu J, Li H. Systematic review and meta-analysis of olfactory and gustatory dysfunction in COVID-19. Int J Infect Dis. 2022;117:155–61.
26. Horwitz LI, Becker JH, Huang W, et al. Olfactory dysfunction after SARS-CoV-2 infection in the RECOVER adult cohort. JAMA Netw Open. 2025;8(9):e2533815.
27. Cristillo V, Pilotto A, Cotti Piccinelli S, et al. Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection. J Am Geriatr Soc. 2021;69(10):2778–80.
28. Lötsch J, Brosig O, Slobodova J, Kringel D, Haehner A, Hummel T. Diagnosed and subjectively perceived long-term effects of COVID-19 infection on olfactory function assessed by supervised machine learning. Chem Senses. 2024;49:bjad051.
29. Morawa E, Krehbiel J, Borho A, et al. Cognitive impairments and mental health of patients with post-COVID-19: a cross-sectional study. J Psychosom Res. 2023;173:111441.
30. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22(1):39–52.
31. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the 'Sniffin' Sticks' including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol. 2007;264(3):237-43.
32. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276(3):719–28.
33. R Core Team. R: a language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing; 2023. Available from: https://www.R-project.org/
34. Ogle DH, Doll JC, Wheeler AP, Dinno A. FSA: simple fisheries stock assessment methods [Internet]. 2026. doi: 10.32614/CRAN.package.FSA
35. Li J, Hu X, Chen L, et al. Olfactory impairment remains three years after COVID-19. Research Square [Preprint]. 2025. Available from: https://doi.org/10.21203/rs.3.rs-7337899/v1
36. Vilarello BJ, Jacobson PT, Tervo JP, et al. Olfaction and neurocognition after COVID-19: a scoping review. Front Neurosci. 2023;17:1198267.
37. Voruz P, Jacot de Alcântara I, Nuber-Champier A, et al. Frequency of abnormally low neuropsychological scores in post-COVID-19 syndrome: the Geneva COVID-COG cohort. Arch Clin Neuropsychol. 2022;38(1):1–11.
38. Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. J Clin Exp Neuropsychol. 2010;32(10):1062–7.
39. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health. 2020;9:100163.
40. Alemanno F, Houdayer E, Parma A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: a COVID-rehabilitation unit experience. PLoS One. 2021;16(2):e0246590.
41. Popa E, Popa AE, Poroch M, et al. The molecular mechanisms of cognitive dysfunction in long COVID: a narrative review. Int J Mol Sci. 2025;26(11):5102.
42. Hosp JA, Reisert M, Dressing A, et al. Cerebral microstructural alterations in post-COVID-condition are related to cognitive impairment, olfactory dysfunction and fatigue. Nat Commun. 2024;15(1):4256.
43. Guo Z, Sun S, Xiao S, et al. COVID-19 is associated with changes in brain function and structure: a multimodal meta-analysis of neuroimaging studies. Neurosci Biobehav Rev. 2024;164:105792.
44. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604(7907):697–707.
45. Muccioli L, Sighinolfi G, Mitolo M, et al. Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction. Neuroimage Clin. 2023;38:103410.
46. Liu DT, Welge-Lüssen A, Besser G, Mueller CA, Renner B. Assessment of odor hedonic perception: the Sniffin' sticks parosmia test (SSParoT). Sci Rep. 2020;10:18019.
47. Hummel T, Fliessbach K, Abele M, et al. Olfactory fMRI in patients with Parkinson's disease. Front Integr Neurosci. 2010;4:125.
48. Parker JK, Methven L, Pellegrino R, Smith BC, Gane S, Kelly CE. Emerging pattern of post-COVID-19 parosmia and its effect on food perception. Foods. 2022;11(7):967.
49. Vance DE, Del Bene VA, Kamath V, et al. Does olfactory training improve brain function and cognition? A systematic review. Neuropsychol Rev. 2024;34(1):155-191.

Moritz Engelhardt
Department of Psychiatry and Psychotherapy
University Hospital
Friedrich-Alexander-Universität
Erlangen-Nürnberg (FAU)
Schwabachanlage 6
91054 Erlangen
Germany

E-mail: Moritz.me.engelhardt@fau.de
ORCID-ID: 0009-0001-1406-852X

Moritz Engelhardt[1], Judith A. Stelzer[1], Regina Herold[2], Evelyne Hanc[2], Eva Morawa[2], Yesim Erim[2,3], Jessica Freiherr[1,4]

[1] Department of Psychiatry and Psychotherapy, University Hospital, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
[2] Department of Psychosomatic Medicine and Psychotherapy, University Hospital, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany
[3] Post COVID Center of the University Hospital of Erlangen, Germany
[4] Sensory Analytics and Technologies, Fraunhofer Institute for Process Engineering and Packaging IVV, Freising, Germany

Rhinology 64: 6, 0 - 0, 2026
https://doi.org/10.4193/Rhin26.029

Received for publication:
January 16, 2026
Accepted: June 20, 2026

Associate Editor:
Basile Landis

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplemental methods

Extended clinical testing routine

All patients of the PCCE were forwarded from a general practitioner and had to meet the WHO criteria for PASC. Independent of this study, patients went through a standard testing routine to confirm PASC and rule out other etiologies, conducted by trained specialists. Results from preceding diagnostics including laboratory analyses, electrocardiography, cardiac ultrasound, and pulmonary function testing were prerequisites. The specialized testing routine included cognitive assessments using the digit span backwards test (DSB) from the Wechsler Memory Scale-Revised for working memory [1], module 1 of the Regensburg Verbal Fluency Test (Regensburger Wortflüssigkeits-Test; RWT) [2], and the d2 Test of Attention (D2) for working speed and attention [3]. Other parts of the testing routine included a psychosomatic examination by trained psychologists, an internal immunological-rheumatological assessment, an ophthalmological examination, and blood sampling.

As patient-reported outcome measures (PROMs), patients filled out health-related questionnaires including the Fatigue Severity Scale (FSS), Insomnia Severity Index (ISI), Somatic Symptom Disorder questionnaire (SSD), DePaul Post-Exertional Malaise Questionnaire (DSQ-PEM), Patient Health Questionnaire 9 (PHQ-9) and Patient Health Questionnaire 15 (PHQ-15), the Generalized Anxiety Disorder Scale (GAD-7), and the Post-COVID syndrome score (PCS score) after Bahmer et al. [4]. Sociodemographic and health-related lifestyle behavioral variables were assessed in questionnaires, including vaccination status and course of acute disease. All factors were incorporated into an interdisciplinary medical note including the times since first infection (TSI) and a final diagnosis.

Extended statistical analysis

All statistical analyses were conducted with R (version 4.3.1) [5]. Non-normal data distribution was assessed for most variables using the Shapiro-Wilk test. Correlations were calculated using Spearman coefficients on pairwise complete observations; P values for bivariate correlations are reported unadjusted. To examine whether cognitive-olfactory associations were independent of respiratory symptoms, partial correlations between olfactory function and cognitive measures were computed controlling for respiratory problems [6].

Due to the convergence of multiple tests and scores from different sources, single data points were missing. To account for this, predictor analysis was preceded by multiple imputation (20 datasets; MICE with predictive mean matching; fixed random seed) implemented in the mice package [7]. Variables redundant with TDI score, subitems of composite scores, variables with zero-variance or many missing values (e.g., PCS score item for exercise intolerance), or items with strong collinearity (e.g., DSQ-PEM) were excluded, leaving 34 predictors. Variable coding and inclusion decisions are detailed in Table S1.

LASSO regression with 10-fold cross-validation (standardized predictors) was performed using glmnet [8], and variables with non-zero coefficients in ≥ 18/20 (≥ 90%) imputed datasets were retained. Final unpenalized linear models were fitted to each imputed dataset and pooled using Rubin's rules using the mice package. To assess complex nonlinear relations, a random forest model was fitted to the imputed datasets using the randomForest package [9], and variable importances were averaged across imputations. Pre-existing conditions potentially affecting olfactory function were documented (Table 1) and assessed for inclusion. Chemotherapy (n=3) and zinc deficiency (n=2) were not modeled due to insufficient prevalence for stable estimation; zinc deficiency was additionally considered unreliable based on self-report and ambiguous in causal direction relative to PASC.

For the analysis of hedonic perception, only valence ratings from trials with a perceived intensity ≥ 2 were included, since ratings of odors that were not perceived were considered non-meaningful. Hedonic range (maximum minus minimum valence rating), upper hedonic limit (maximum valence rating), and lower hedonic limit (minimum valence rating) were computed per participant from perceived odors. Anosmic patients (n = 6) were not included because of insufficient sample size for stable estimates, ten patients were excluded due to missing TSI or rating values, and six further patients were excluded casewise due to missing covariate values, yielding 122 patients (df = 115) in the hedonic models. Linear models were fitted with the hedonic parameter as target and OD group as predictor, alongside age, sex, TSI, parosmia, and anhedonia as covariates. Anhedonia (PHQ-9 item 1) was included given its documented association with sensory hedonic perception [10]. For the hedonic summary metric models, bootstrap confidence intervals (5000 iterations, BCa method) were used to account for non-normally distributed residuals; t and P values were model based. Post-hoc pairwise comparisons were conducted using estimated marginal means (EMMs) with Bonferroni-Holm correction using the emmeans package [11].

Linear mixed models from the lme4 package [12] were used to assess odor-level effects. A model was fitted with valence rating as target, a fixed-effects interaction between OD group and odor item, age, sex, TSI, parosmia, anhedonia, and trial-level intensity rating as a covariate to isolate hedonic from intensity effects,

and participant as random intercept. The OD×odor interaction was marginal (P = .06); per-odor contrasts from this model are therefore reported as exploratory. Per-odor contrasts (hyposmic vs. normosmic) were Bonferroni-Holm corrected across the 16 odors. An analogous model using the continuous TDI-PR score in place of OD groups showed a significant interaction (P = .04). Effect sizes (Cohen's d) were computed for each pairwise contrast using the residual standard deviation of the model as the standardizer. All regression models were checked for residual normality, homoscedasticity, multicollinearity, and influential observations.

References

1. Härting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J. Wechsler Memory Scale – Revised Edition, German Edition. Bern: Huber, 2000.
2. Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test (RWT). Göttingen: Hogrefe, 2001.
3. Brickenkamp R, Schmidt-Atzert L, Liepmann D. Test d2-Revision: Aufmerksamkeits- und Konzentrationstest. 1st ed. Göttingen: Hogrefe, 2010.
4. Bahmer T, Borzikowsky C, Lieb W, et al. Severity, predictors and clinical correlates of Post-COVID syndrome (PCS) in Germany: a prospective, multi-centre, population-based cohort study. EClinicalMedicine 2022; 51: 101549.
5. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2023. Available from: https://www.R-project.org/
6. Hervé M. RVAideMemoire: testing and plotting procedures for biostatistics. R package version 0.9-83-12. 2025. Available from: https://CRAN.R-project.org/package=RVAideMemoire
7. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011; 45(3): 1-67.
8. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw 2010; 33(1): 1-22.
9. Liaw A, Wiener M. Classification and regression by randomForest. R News 2002; 2(3): 18-22.
10. Utz KS, Martini M, Mrochen A, et al. A multisensory deficit in the perception of pleasantness in Parkinson's disease. J Parkinsons Dis 2021; 11(4): 2035-2045.
11. Lenth RV, Piaskowski J. emmeans: estimated marginal means, aka least-squares means. R package version 2.0.3. 2026. Available from: https://rvlenth.github.io/emmeans/
12. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015; 67(1): 1-48.

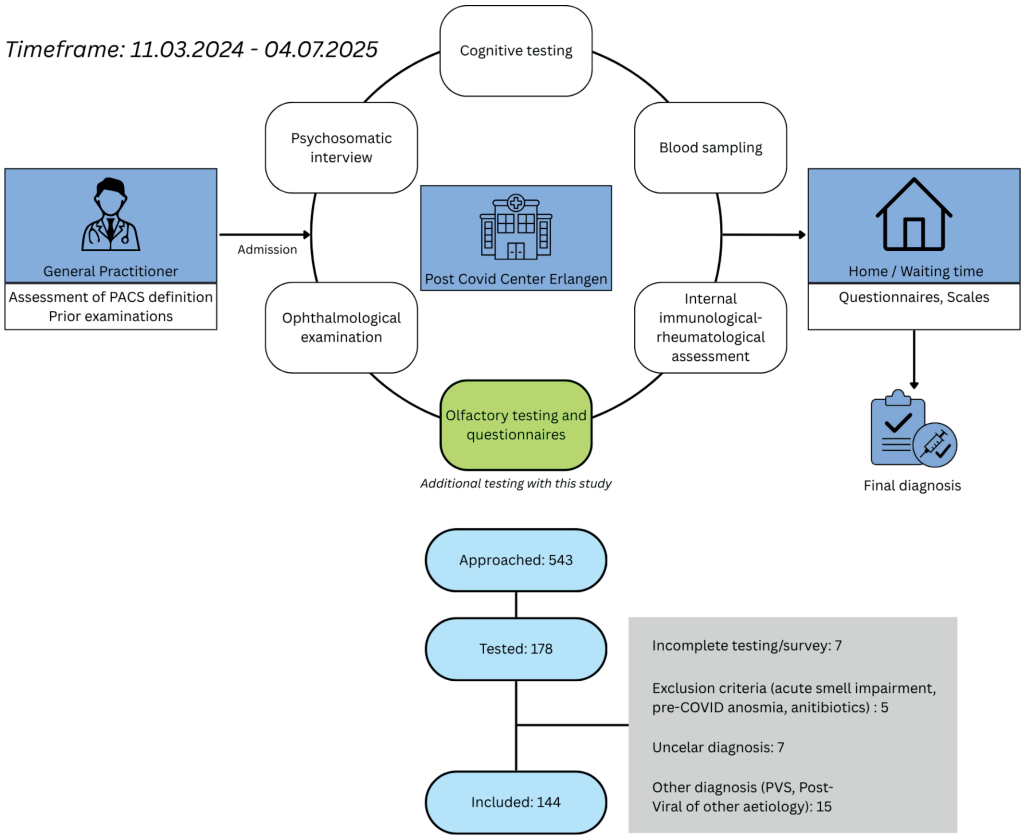


Figure S1. Testing scheme and exclusion procedure for this study. Patients were forwarded from a general practitioner, completed a testing sequence at the Post-COVID-Center Erlangen, and filled out questionnaires and scales at home or in between tests. The olfactory testing regimen (green) was included in the existing testing procedure of the Post-Covid-Center Erlangen. 543 patients were approached for the olfactory testing in a timeframe from March 2024 to July 2025, of which 178 were tested and 144 were included for the analysis.

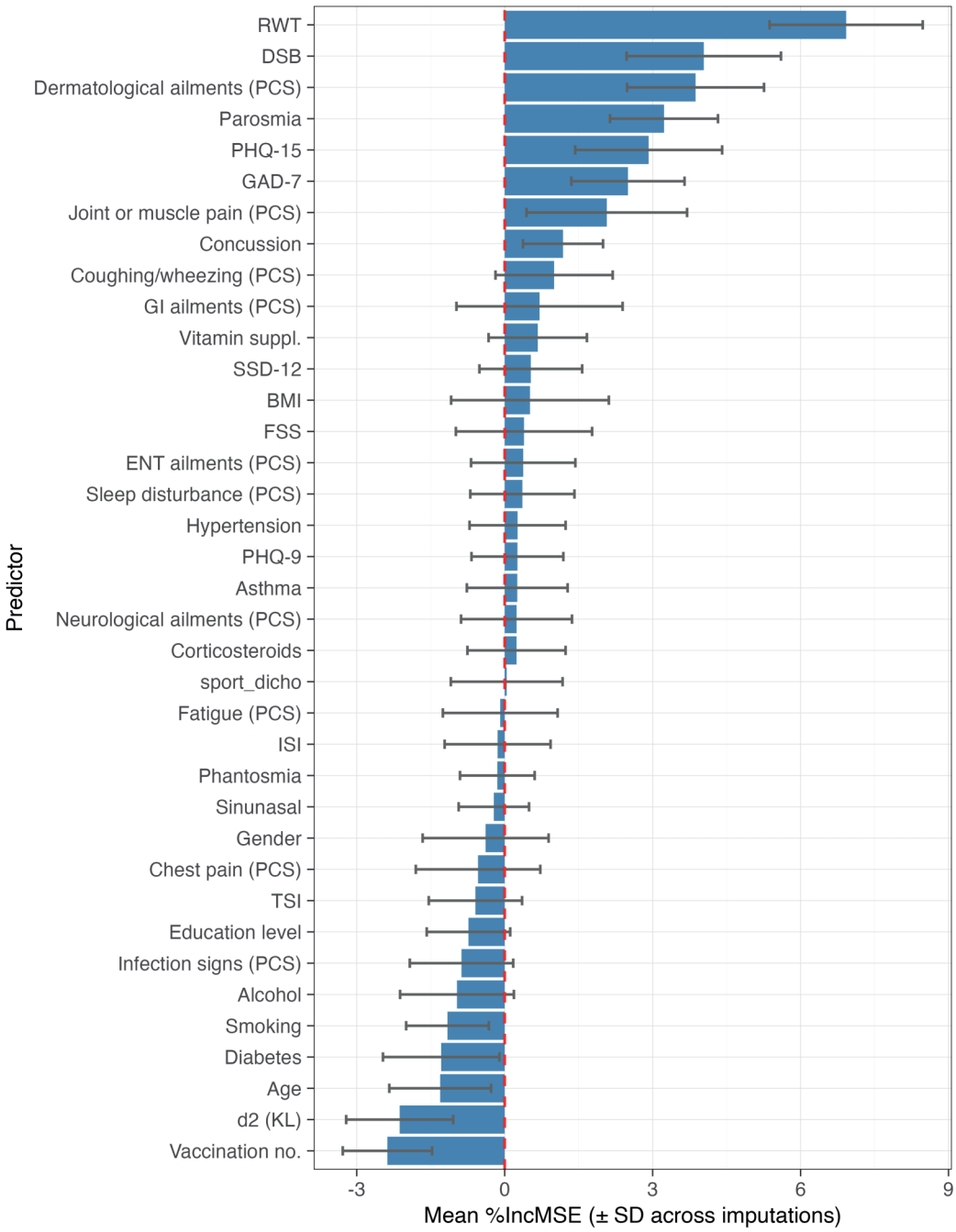


Figure S2. Feature ranking after highest mean importance (%IncMSE) with error bars showing standard deviation (SD) from random forest modelling without importance threshold.

Table S1. List of predictors for LASSO and random forest analysis with TDI-PR as outcome measure.

Predictor	Used	Inclusion coding / Exclusion reason
PAR	LASSO+RF	Yes/No
PHANT	LASSO+RF	Yes/No
Age	LASSO+RF	
Gender	LASSO+RF	
Education	LASSO+RF	
BMI	LASSO+RF	
Exercise	LASSO+RF	Dichotomized (Never - at least 1x per week)
Smoking	LASSO+RF	Dichotomized (Never/Former smoker - Sometimes or more often)
Alcohole	LASSO+RF	Dichotomized (1x per months or less/never - 1x per months)
TSI	LASSO+RF	
COD	Not used	Insufficient variability (85% in 'home' group)
Vaccination number	LASSO+RF	
Diabetes	LASSO+RF	
Hypertension	LASSO+RF	
Supplements	LASSO+RF	
Corticosteroids	LASSO+RF	
Sinunasal comorbidities	Regression+RF	Forced covariate instead of LASSO selection
Asthma	Regression+RF	Forced covariate instead of LASSO selection
Concussion	Regression+RF	Forced covariate instead of LASSO selection
Zinc deficiency	Not used	Insufficient prevalence (n=2), uncertain self-report, confounder versus PASC-mediated consequence
Chemotherapy	Not used	Insufficient prevalence (n=3)
SOF (baseline, acute, current)	Not used	Subjective/retrospective assessment of outcome measure
RWT	LASSO+RF	
DSB	LASSO+RF	
D2 (KL)	LASSO+RF	
D2 (BZO)	Not used	Collinearity with D2 (KL)
PHQ-9	LASSO+RF	
PHQ-15	LASSO+RF	
GAD-7	LASSO+RF	
SSD	LASSO+RF	
FSS	LASSO+RF	
ISI	LASSO+RF	
PEM	Not used	Collinearity with FSS
CRP	Not used	Excessive missingness; near-zero variance
PCS: Fatigue	LASSO+RF	
PCS: Muscle/joint pain	LASSO+RF	
PCS: ENT ailments	LASSO+RF	
PCS: Respiratory symptoms	LASSO+RF	
PCS: Chest pain	LASSO+RF	
PCS: Gastrointestinal ailments	LASSO+RF	
PCS: Neurological ailments	LASSO+RF	
PCS: Dermatological ailments	LASSO+RF	
PCS: Infection signs	LASSO+RF	
PCS: Sleep disturbance	LASSO+RF	
PCS: Exercise intolerance	Not used	Conceptual overlap with other PCS items; extreme group imbalance (5 vs. 128)

TDI-PR: Olfactory function as Sniffin' Sticks Threshold-Discrimination-Identification score standardized on age- and sex-matched normative data; PAR: Parosmia; PHANT: Phantosmia; TSI: time since acute infection; COD: course of disease; SOF: Subjective Olfactory Function; RWT: Regensburg Verbal Fluency Test; DSB: Digit span backward test for working memory; D2: d2 test of attention; KL: Number of correctly marked d2-symbols minus the number of incorrectly marked symbols; BZO: Number of processed target objects; PHQ-9: Patient Health Questionnaire with 9 items; PHQ-15: Patient Health Questionnaire with 15 items; GAD-7: Generalized Anxiety Disorder Scale; SSD: Somatic Symptom Disorder scale; FSS: Fatigue Severity Scale; ISI: Insomnia Severity Index; PEM: Post-Exertional Malaise questionnaire; CRP: C-Reactive Protein; PCS: Post-Covid-Score

Table S2. Comparison of linear models with TDI-PR as dependent variable, LASSO-selected parameters as predictors, with and without comorbidities as forced covariates.

Predictor	B (without)	P (without)	B (with)	P (with)
Parosmia (yes)	-7.64	0.083	-7.70	0.083
Respiratory symptoms (PCS)	-8.04	0.051	-8.41	0.042
Verbal fluency (RWT)	0.16	0.040	0.16	0.039
Working memory (DSB)	0.05	0.391	0.06	0.309
Corticosteroids (yes)	13.56	0.136	-0.80	0.946
Muscle/joint pain (PCS)	-8.72	0.090	-9.43	0.070
Dermatological ailments (PCS)	9.67	0.015	9.48	0.019
PHQ-15	-0.51	0.191	-0.46	0.252
Sinunasal (comorbidity)			0.83	0.875
Asthma (comorbidity)			13.92	0.067
Concussion (comorbidity)			-5.30	0.375

Abbreviations: TDI-PR: olfactory function as Sniffin' Sticks test score standardized on age- and sex corrected normative data; RWT: verbal fluency test (Regensburg Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward); PCS: Post-COVID-Score; PHQ-15: Patient Health Questionnaire – 15 items

Table S3. Selective spearman correlation between olfactory test (TD-PR) and subtests (Threshold, Discrimination, Identification) with selected cognitive domain tests (RWT, DSB).

Cognitive measure	Olfactory measure	Spearman rho	P value	N
Working memory	TDI percentile rank	0.209	0.015	135
Working memory	TDI score	0.203	0.018	135
Working memory	Threshold	0.133	0.123	135
Working memory	Discrimination	0.167	0.053	135
Working memory	Identification	0.103	0.235	135
Verbal fluency	TDI percentile rank	0.176	0.04	137
Verbal fluency	TDI score	0.15	0.08	137
Verbal fluency	Threshold	0.125	0.146	137
Verbal fluency	Discrimination	0.104	0.228	137
Verbal fluency	Identification	0.039	0.651	137

Abbreviations: TDI-PR: olfactory function as Sniffin' Sticks test score standardized on age- and sex corrected normative data; RWT: verbal fluency test (Regensburg Wortflüssigkeits-Test); DSB: working memory test (Digit Span Backward).

Table S4. Association between olfactory function (TDI-PR) and hedonic summary metrics (linear models).

Hedonic metric	B	CI (2.5%)	CI (97.5%)	T	P
VAL - max	0.009	0.001	0.018	2.12	0.036
VAL - min	0.009	-0.001	0.019	1.84	0.068
Hedonic range	0.000	-0.013	0.014	0.03	0.975
Hedonic SD	-0.003	-0.008	0.002	-1.08	0.284

B: unstandardized regression coefficient for TDI-PR. VAL - max: maximum valence rating; VAL - min: minimum valence rating.

Table S5. Association between olfactory function (TDI-PR) and maximum valence (linear models).

Parameter	B	CI (2.5%)	CI (97.5%)	T	P
OD (L)	0.375	0.083	0.666	2.55	0.012
Age	0.007	-0.012	0.025	0.72	0.475
Sex (m)	- 0.784	-1.208	0.361	-3.67	< 0.001
TSI	- 0.009	-0.027	0.010	-0.91	0.367
Parosmia (yes)	0.153	-0.297	0.604	0.67	0.502

B: unstandardized regression coefficient; OD: olfactory dysfunction group; m: male sex; TSI: time since first infection.

Table S6. Slope of olfactory function (percentile rank) on hedonic valence per odor from linear mixed model analysis, adjusted for intensity, age, gender, time since infection, parosmia, and anhedonia status. P (Holm): Bonferroni-Holm-corrected for 16 comparisons. P (uncorr.): uncorrected. Positive slopes indicate higher valence ratings with better olfactory function.

Odor	B	SE	t	CI (2.5%)	CI (97.5%)	P
Garlic	0.025	0.009	2.721	-0.002	0.052	0.007
Coffee	0.025	0.009	2.716	-0.002	0.053	0.007
Cloves	0.02	0.009	2.102	-0.008	0.047	0.036
Leather	0.018	0.009	1.965	-0.009	0.046	0.050
Anise	0.011	0.01	1.2	-0.017	0.040	0.230
Fish	0.011	0.009	1.157	-0.017	0.038	0.247
Peppermint	-0.01	0.009	-1.086	-0.037	0.017	0.278
Banana	0.008	0.009	0.857	-0.019	0.035	0.392
Licorice	0.008	0.009	0.87	-0.020	0.036	0.384
Rose	-0.006	0.009	-0.661	-0.034	0.021	0.509
Lemon	0.005	0.01	0.489	-0.024	0.033	0.625
Turpentine	0.005	0.01	0.571	-0.023	0.034	0.568
Orange	0.004	0.009	0.469	-0.023	0.032	0.639
Apple	0.004	0.009	0.447	-0.023	0.032	0.655
Pineapple	0.003	0.009	0.301	-0.025	0.030	0.763
Cinnamon	-0.001	0.009	-0.069	-0.028	0.027	0.945