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Functional olfactory impairment and fatigue in post-COVID-19 syndrome including ME/CFS – a longitudinal prospective observational study

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ABSTRACT

Post-COVID-19 syndrome (PCS) affects a significant proportion of individuals, with olfactory impairment and fatigue as prominent long-term symptoms. A subset of PCS patients with pronounced fatigue meets the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), here referred to as PCS-ME/CFS. This study explores the relationship between PCS, fatigue, and olfactory function, and investigates the potential of olfactory impairment as a diagnostic and prognostic marker.

We assessed olfactory function up to 28 months post-COVID-19 in 45 PCS patients (22 PCS, 23 PCS-ME/CFS) using the extended Sniffin' Sticks test, which evaluates odor threshold, discrimination, and identification, providing a composite score. Fatigue severity and health-related quality of life were assessed using validated questionnaires, a standardized test measured cognitive function, and handgrip strength indicated physical fatiguability.

Both PCS and PCS-ME/CFS patients showed significant improvement in olfactory function, with all patients returning to normosmia after 20 months, regardless of diagnosis. While odor threshold was the most affected olfactory measure in Sniffin' Sticks testing, odor identification was the only measure that remained impaired over time. Olfactory impairment correlated with cognitive, physical, and mental performance, with stronger correlations in the PCS group, particularly linking better odor discrimination at baseline to improved daily functioning and health-related quality of life after 20 months.

Our findings suggest that odor identification assessed in standardized testing may remain impaired the longest in patients with persisting symptoms after COVID-19, reflecting persisting central processing difficulties. Correlations between olfactory performance, cognitive function, and physical ability point to shared underlying

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mechanisms. Early olfactory improvements may be linked to better long-term cognitive outcomes, highlighting a possible prognostic role of olfactory function in these patients.

1. Introduction

The post-COVID-19 syndrome (PCS) affects approximately 10–30 % of patients who have recovered from mild or moderate COVID-19 infections, although prevalence varies depending on the study and population. With the continued global presence of COVID-19, particularly among young working adults, PCS remains a major challenge to health care systems and societies worldwide (Ballering et al., 2022; Davis et al., 2023). The World Health Organization (WHO) defines PCS as a condition characterized by a wide range of symptoms that appear following an acute SARS-CoV-2 infection and typically manifest within three months, persist for at least two months, and cannot be attributed to other medical causes. According to WHO, symptoms are known to relapse and fluctuate over time and may affect multiple organ systems (WHO, 2022), with olfactory impairment, cognitive dysfunction and fatigue among the most prominent long-term sequelae (Sivan and Taylor, 2020; Stavem et al., 2021). Additional symptoms may include shortness of breath, chest pain, muscle pain, headaches, and palpitations.

Odor dysfunction, reported in 19 % and 55 % of acute COVID-19 cases (Lechien et al., 2023; Speth et al., 2022), typically resolves within 14 days, with most recovering within one to two months (Dias et al., 2024; Lechien et al., 2021). However, 5–20 % experience persistent olfactory impairment (Boscolo-Rizzo et al., 2023; Santos et al., 2021; Sharetts et al., 2024), which can severely impact well-being and daily functioning. While several studies have investigated olfactory function in patients with COVID-19 and PCS, few have employed standardized psychophysical testing, which is essential for accurate assessment of olfactory function, given the unreliability of self-reported data (Philpott et al., 2006). Comprehensive otolaryngological exams are also essential, as olfactory disturbances are common in the general population and often linked to sinonasal disease (Damm et al., 2004). Research suggests that SARS-CoV-2 primarily affects odor thresholds, with less impact on odor identification or discrimination (Boscolo-Rizzo et al., 2021, 2023). To provide a comprehensive assessment of all facets of olfactory function, we employed the extended three-stage Sniffin' Sticks test in this study (Hummel et al., 1997).

Previous studies from our group have shown that a subset of PCS patients develop myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is a disabling disease characterized by more severe and persistent symptoms compared to those with PCS alone (Legler et al., 2023). ME/CFS is a complex, multisystemic disorder marked by two key features: post-exertional malaise (PEM), a worsening of symptoms following physical or mental exertion, and profound, persistent fatigue (Jason et al., 2015).

Early in the COVID-19 pandemic, researchers began linking smell impairment to cognitive decline and fatigue in patients with mild COVID-19 (Cristillo et al., 2021; Llana et al., 2023), and later also in patients with persistent symptoms post-infection (Muccioli et al., 2023; Campabadal et al., 2023; Vance et al., 2024; Shahbaz et al., 2025). Azcue et al. compared cognitive outcomes, neuropsychiatric symptoms, and general somatic symptoms in 42 ME/CFS and 73 PCS patients (Azcue et al., 2022), with mean disease durations of 12 months for PCS patients and 85 months for ME/CFS patients. Their findings and those from other studies propose a potential link between olfactory dysfunction and various PCS symptoms, including increased risk of cognitive deficits, "brain fog", and headaches (Azcue et al., 2022, 2024; Di Stadio et al., 2022; Fatuzzo et al., 2023). Beyond the context of viral illness, large population studies in healthy adults have also demonstrated an association between superior olfactory performance and enhanced cognitive function, particularly in domains such as verbal abilities, semantic memory, verbal learning, verbal memory, attention, cognitive processing speed, and executive function (MacDonald et al., 2018; Yahiaoui-Doktor et al., 2019). These findings collectively underscore a strong neurological link between olfaction and cognition and raise the possibility that olfactory impairment could serve as a marker of broader neurological involvement. Specifically, olfactory impairment has long been recognized as an early indicator of neurodegenerative diseases (Devanand et al., 2015; Fatuzzo et al., 2023; Schubert et al., 2013; Yaffe et al., 2017).

Building on these findings, our study aims to examine the long-term involvement of the olfactory system in PCS patients who also meet the criteria for ME/CFS, compared to those with PCS alone. Additionally, we seek to explore the long-term impact of COVID-19 on all domains of olfactory function, assessing its potential as both a diagnostic and prognostic marker for PCS and related adverse outcomes, as well as its interaction with other symptoms of PCS.

2. Methods

2.1. Study cohort

This research utilized data from the PA-COVID study (DRKS-ID DRKS00021688) conducted at the Charité - Universitätsmedizin Berlin, approved by the institution's ethics committee in accordance with the 1964 Declaration of Helsinki and its subsequent amendments (approval number EA2/006/20). The current analysis examines a subset of data from a prospective observational cohort of adult patients (above 18 years) experiencing moderate to severe fatigue and exertion intolerance following PCR- or antibody-confirmed COVID-19 diagnosis. All participants met the diagnostic criteria for PCS, with a subset additionally fulfilling the criteria for ME/CFS.

To ensure clear attribution of olfactory changes to COVID-19, we excluded individuals with pre-existing smell impairments, chronic rhinosinusitis, or a history of sinonasal surgeries known to affect olfaction (Fokkens et al., 2020). However, eight patients who had previously undergone minor ear, nose, and throat (ENT) procedures - such as adenectomies or radiofrequency therapy of nasal concha - were included. These interventions are generally not associated with olfactory impairment. Each of these patients underwent a thorough ENT examination by otolaryngologists, including nasal endoscopy, to rule out any structural abnormalities. Importantly, no structural ENT-related cause of olfactory dysfunction was identified in these patients or in any other participants in the cohort.

In this real-world study, all patients attending Charité's post-COVID center underwent a standardized diagnostic protocol, which included neurological assessments, immunological analyses, and, when clinically indicated, pulmonological and cardiological examinations, as previously described (Kedor et al., 2022; Legler et al., 2023). The study design included study and follow-up visits at 6–9 months, 10–20 months and more than 20 months after the initial COVID-19 diagnosis.

SARS-CoV-2 variants were assigned based on the variant peak prevalences in Germany, using data from CoVariants.org (Emma, 2021). Patients infected between August 2020 and January 2021 were infected with the wildtype variant. From February 2021 to mid-June 2021, the Alpha variant predominated, followed by the Delta variant, which was most common until mid-January 2022. From mid-January 2022 onward, the Omicron variant became predominant in Germany.

2.2. PCS and ME/CFS diagnosis

PCS was diagnosed according to the WHO criteria, which define the condition as the presence of ongoing or new symptoms that emerge

within three months of acute SARS-CoV-2 infection and persist for at least two months (World Health Organization, 2022). The diagnosis of ME/CFS was based on the Canadian Consensus Criteria (CCC), which emphasize the presence of severe, persistent PEM lasting at least 14 h. PEM is considered a key distinguishing feature of ME/CFS, differentiating it from other forms of predominantly secondary illness-related fatigue (Jason et al., 2015). In addition to fatigue, sleep dysfunction and pain are mandatory diagnostic criteria. Furthermore, at least two specific neurological or cognitive manifestations are required, as well as at least one manifestation from two of either autonomic, neuroendocrine, or immune systems.

2.3. Olfactory assessment

Olfactory function was assessed using the extended Sniffin' Sticks test, also known as the Threshold-Discrimination-Identification (TDI) test, a validated and widely used method that measures three key components of olfaction: odor threshold (T), discrimination (D), and identification (I). The test is conducted using pen-like devices containing odorants and provides an overall evaluation of olfactory performance (Hummel et al., 2007).

The Threshold test determines the lowest odor concentration a participant can detect, using 16 concentrations of 2-phenylethanol (rose scent) prepared in a 1:2 dilution series. The highest concentration used was 4 % 2-phenylethanol diluted in propylene glycol, and the lowest was 0.0001263 %. The test includes 16 sets of "pen triplets"; in each triplet, two pens contain only the solvent, while the third contains the rose odor. Concentration increases across the sets. To ensure unbiased results, participants wore sleep masks. After smelling each triplet, they used a "forced-choice" method to identify which pen contained the odorant. The Discrimination test evaluates perceptual discrimination between odors. It consists of 16 triplets of odorized pens. In each triplet, two pens contain the same scent, while the third contains a different, "odd" odor. All odors were suprathreshold and matched in intensity. The triplets were randomized and presented individually, with a 3-s interval between pens and a 30-s interval between triplets. One point was awarded for each correct identification. The Identification test assesses the ability to recognize and name odors. It includes 16 pens, each containing a distinct suprathreshold odor commonly encountered in daily life. In this test set, odors included: orange oil, leather fragrance, cinnamaldehyde, peppermint oil, banana fragrance, citrus oil, licorice fragrance, turpentine, garlic fragrance, coffee oil, apple fragrance, clove oil, pineapple aroma, rose perfume oil, anethole, and fish odor – all diluted in diethylphtalate and propylene glycerol. For each odor presentation, participants were shown a card with four multiple-choice options and asked to select the correct one. They were allowed to sample the pens as often as needed. One point was awarded per correct answer. Each subtest is scored from 0 to 16, resulting in a composite TDI score ranging from 0 to 48.

Hyposmia were defined based on age-dependent TDI score cut-offs, as established in prior research and shown in Supplementary Table 1. The cut-off for anosmia is age-independent, defined as a total TDI score below 16.5 (Hummel et al. 1997, 2007). These terms describe quantitative olfactory disorders, referring to a reduction (hyposmia) or complete absence (anosmia) of the sense of smell. Olfactory function is typically classified as normosmia, hyposmia, or anosmia: Normosmia indicates normal smell perception and identification. Hyposmia refers to reduced olfactory sensitivity, with odors perceived as less intense. Anosmia denotes a complete loss of smell, impairing odor perception in daily life.

Since only three patients were diagnosed with anosmia (PCS n = 1, PCS-ME/CFS n = 2), they were grouped with patients with hyposmia to facilitate statistical analysis. Additionally, participants were asked to self-report their perceived smell impairment during the acute phase of COVID-19 infection and at their most recent follow-up visit, allowing for a comparison between subjective experience and objective measurements.

2.4. Questionnaires and clinical outcome measures

2.4.1. Chalder Fatigue Scale

Fatigue severity was assessed using the Chalder Fatigue Questionnaire (CFQ), an 11-item scale scored on a Likert scale ranging from 0 to 3 for each item. The total CFQ score ranges from 0 (no fatigue) to 33 (severe fatigue). The CFQ also allows differentiation between mental and physical fatigue, with sub-scores based on 4 items related to mental fatigue and 7 items related to physical fatigue (Morriss et al., 1998). This questionnaire is widely used due to its sensitivity in capturing the multifaceted nature of fatigue in chronic conditions.

2.4.2. Bell Score

To measure the impact of chronic fatigue on daily functioning, we used the Bell Score. The Bell Score provides a measure of the degree to which fatigue affects everyday activity. A score over 80 indicates minimal impairment, while a score of 50 reflects moderate symptoms at rest and moderate to severe symptoms after mental or physical exertion, limiting the patients to light activities such as desk work for 4–5h per day. A low Bell Score of 0–20 indicates severe disability, often confining patients to bed due to debilitating fatigue. The Bell Score serves as a tool for characterizing the severity and functional impact of fatigue patients (Bell, 1995).

2.4.3. Symbol Digit Modality Test-90 (SDMT-90)

We used the SDMT-90 to assess cognitive impairment and processing speed. This test is designed to evaluate sustained attention, visual scanning, and information processing speed, which are crucial cognitive domains often affected in various neurological conditions. In the SDMT-90, patients are shown a key that pairs nine abstract symbols with numbers from 1 to 9. Participants then have 90 s to match as many symbols as possible with their corresponding numbers. The score is based on the number of correct symbol-digit pairings completed within the 90-s period, with a maximum possible score of 110. Higher scores indicate better cognitive functioning. The SDMT has demonstrated high sensitivity and reliability in detecting cognitive dysfunction in various neurological conditions. Its ability to track cognitive performance over time makes it a valuable tool for longitudinal assessments of cognitive changes (Strober et al., 2020).

2.4.4. Short Form-36 (SF-36)

Health-related quality of life (HRQoL) was assessed using the well-established and validated SF-36 Health Survey, which evaluates multiple domains of physical and mental well-being. The eight subscales include physical functioning, social functioning, general health perceptions, emotional well-being, and physical pain. Scores for each subscale range from 0 to 100, with 0 indicating the greatest possible limitation and 100 representing no relevant health limitations (Ware and Sherbourne, 1992). The SF-36 is recognized for its cross-disease applicability and its ability to provide a comprehensive overview of patients' HRQoL.

2.4.5. Patient health Questionnaire-9 (PHQ-9)

We used the PHQ-9 as a screening tool for depressive symptoms, given the high comorbidity of depression in individuals with chronic illnesses such as ME/CFS. The PHQ-9 consists of 9 items, each scored on a scale from 0 to 3, assessing the frequency of depressive symptoms over the past two weeks. A total score under 5 suggests no clinically relevant depressive symptoms, while scores between 20 and 27 indicate severe depressive symptoms (Gräfe et al., 2004).

2.5. Handgrip strength (HGS)

To assess muscle exertion and fatigability, we employed HGS testing

using an electronic dynamometer. HGS is a reliable measure of overall muscle strength and endurance, making it particularly useful for evaluating physical functioning and fatigue. Participants were asked to squeeze a hand-held dynamometer with their dominant hand ten times at maximum effort. This was repeated once more after a 60-min rest interval between sets. The maximum force (fmax1, fmax2) and average force (fmean1, fmean2) for each set of ten squeezes were recorded in kilograms. These measures were compared with reference values established by Jäkel et al. for patients with ME/CFS, allowing for the evaluation of the muscle fatigue ratio and recovery capacity (Jäkel et al., 2021). The fatigue ratio reflects muscle fatiguability, indicated by a decline in force across repeated measurements. Impaired recovery capacity is reflected by reduced force output during the second measurement, indicating diminished muscle recovery (see Jäkel et al., 2021 for reference values and ratio calculation).

2.6. Statistical analysis

Data for this study were collected and managed using REDCap, an electronic data collection system, with the latest access on May 07th, 2024. We employed non-parametric rank-based ANOVA tests to analyze factorial longitudinal data (Noguchi et al., 2012). Group effects, time effects, and the interaction between group and time effects were analyzed. A group effect refers to a notable difference in the data distribution between the groups under comparison, while a time effect indicates a significant change in the distribution of data over time. An interaction effect reflects a difference in temporal trends between the groups tested. The underlying effect measure is an adaption of the well-known Wilcoxon-Mann-Whitney effect for longitudinal data (see Supplementary Table 2). It can be interpreted as follows: An effect of ½ suggests that the values in one group are approximately equal to those in the combined sample. For example, if group 1's effect is smaller than that of group 2, group 1's values tend to be smaller than those of group 2. These effects were empirically calculated using joint ranks of the data and classical rank-based tests. Effect measures are presented alongside their 95 % confidence intervals. The confidence intervals were estimated using B = 1000 bootstrap samples (Supplementary Table 2).

Furthermore, we conducted rank-based (Spearman) correlation

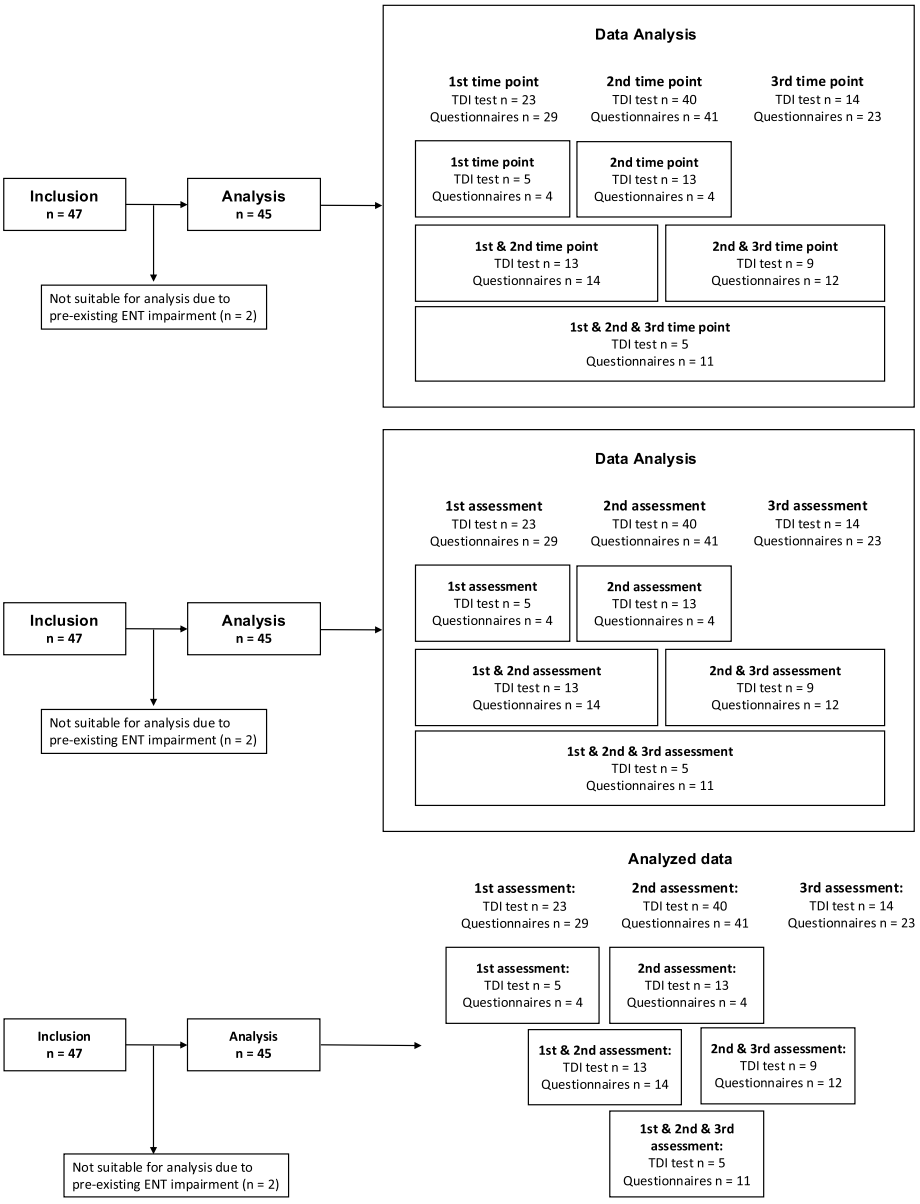

Fig. 1. Participant inclusion and study design. Participant flow chart depicting exclusions during the screening and available data for each of the three assessment periods.

analyses. P-values <0.05 were considered statistically significant. Due to the exploratory nature of this study and the wide range of parameters examined, the main analysis results were not adjusted for multiple comparisons. All data analyses were carried out in Prism version 9 and R version 4.4.0, utilizing the tidyverse version 2.0 and nparLD version 2.2 packages.

3. Results

3.1. Cohort characteristics

This study evaluated olfactory function in 45 individuals with PCS experiencing moderate to severe fatigue and exertion intolerance as their primary post-COVID-19 symptoms (Fig. 1). Of these participants, 23 fulfilled the diagnostic criteria for ME/CFS. The longitudinal follow-up spanned 6–28 months post SARS-CoV-2 infection, stratified into three distinct follow-up periods: below 10 months, 10–20 months and above 20 months post infection. This design allowed assessment of evolution of olfactory function over time. 40 of 45 participants were infected with the SARS-CoV-2 wild type during the first COVID-19 wave and were unvaccinated prior to infection. For detailed information on patient attrition and demographics, see Table 1.

3.2. Evolution of olfactory function

32 participants (71 %, 16/22 PCS, 16/23 PCS-ME/CFS) self-reported olfactory impairment during their acute SARS-CoV-2 infection. While PCS-ME/CFS patients were more severely affected by hyposmia/anosmia in the first months after SARS-CoV-2 infection (PCS-ME/CFS: 45 % [5/11] vs. PCS: 8 % [1/12]), all participants evaluated after 20 months were normosmic (Fig. 2). However, between 10 and 20 months post-infection, 63 % of PCS-ME/CFS (12/19) and 74 % of PCS (14/19) patients still experienced hyposmia (Fig. 2). This evolution reflects significant improvement over time in both groups. Six participants (of 13) complained of parosmia beyond 20 months post-infection (third assessment period), even though they were normosmic according to TDI testing. Among these participants with parosmia, four were diagnosed with PCS-ME/CFS and two with PCS; all were female, and we assumed they were infected with the wild type SARS-CoV-2 variant based on the respective infection period (Emma, 2021).

Olfactory functions were similarly impaired in both PCS and PCS-ME/CFS patients following SARS-CoV-2 infection. Olfactory threshold detection was the most impaired smell property, particularly during the early period post-infection. Both groups showed significant improvement over time in overall olfactory function, as well as in the sub-properties of odor discrimination and threshold detection. The observed improvement in olfactory function became apparent only beyond 20 months after infection. Only odor identification did not improve significantly. Comparing PCS and PCS-ME/CFS patients, no significant group differences or differences in the dynamic of improvement were found during the course of the study (Fig. 3). Further analysis of olfactory sub-properties revealed distinct patterns between patient groups. In the PCS-ME/CFS group, odor identification continued to worsen in the first 20 months before returning to the initial levels. In contrast, the PCS group showed continuous, albeit non-significant, improvement in odor identification. This is particularly interesting considering that both groups demonstrated a significant improvement in odor discrimination and threshold detection over time (Fig. 3).

Table 1
Demographic cohort characteristics. Age is presented as the group means and standard deviation. All other parameters are presented as n per diagnosis group.

	PCS, n = 22	PCS-ME/CFS, n = 23
Sex (female)	18	20
Age (years)	49 (9.8)	51 (11.2)
Type I aeroallergies	12	12
Minor nasal procedures	3	5
SARS-CoV-2 variants according to infection periods		
● Wildtype	14	21
● Alpha B.1.1.7	3	–
● Delta B.1.617.2	3	1
● Omicron B.1.1.529	2	1
COVID-19 vaccination before infection	3	2
COVID-19 vaccination before first follow-up	10	12

3.3. Impact of smell impairment during the acute infection, vaccination status, and virus variant on long-term olfactory function

Most patients, except for five, were not vaccinated against COVID-19 prior to their SARS-CoV-2 infection, with vaccination status being equally distributed across patient groups. However, an additional 17 patients received at least one vaccination before their first olfactory examination. None of the patients who had been vaccinated prior to infection were diagnosed with hyposmia or anosmia, and they demonstrated greater olfactory capabilities compared to the unvaccinated individuals at the initial assessment. Due to the small size of the vaccinated group, however, no significant conclusions can be drawn. The positive effect of COVID-19 vaccination on olfactory function was also at least partially evident when vaccination was administered during the first months post-infection (before the initial assessment): Vaccinated patients (49 % of all patients) showed superior odor discrimination (see Supplementary Fig. 1).

The majority of patients (78 %) was infected with the wildtype variant of SARS-CoV-2, which limited the ability to assess the impact of the virus variant on olfactory function. Among those affected with a later variant (Alpha B.1.1.7, Delta B.1.617.2, Omicron B.1.1.529; n = 10), a smaller number experienced hyposmia/anosmia. Specifically, of the wildtype-infected patients, 56 % (5/9) exhibited hyposmia at the initial assessment, compared to 25 % (2/8) of those infected with a later variant (one of whom was diagnosed with anosmia; see Supplementary Fig. 2).

No significant group differences in olfactory outcomes were found when comparing self-reported olfactory dysfunction to normosmia during acute COVID-19 (see Supplementary Fig. 3).

3.4. Link between cognitive, mental and physical performance and olfactory functions

To assess the potential of olfactory dysfunction as a diagnostic marker for adverse outcomes in PCS, we investigated its correlations with cognitive, mental, and physical performance measures in an explorative fashion. HGS is a known indicator of mortality risk, physical fitness, and an indirect marker of cognitive function. In the PCS group, we found a negative correlation between early post-infection odor threshold recognition and muscle fatigability between 10 and 20 months post-infection. We also observed a positive correlation between muscle recovery and olfactory performance (total olfactory scores and odor discrimination) in the second assessment period (Fig. 4). Hyposmia and anosmia were both negatively associated with muscle recovery (Fig. 4). Mean and maximal HGS demonstrated similar patterns (Fig. 4). Notably, improved muscle recovery early after infection correlated with better odor identification in the second year of PCS. In the PCS-ME/CFS group, we found positive correlations between early odor threshold recognition and overall olfactory performance and future mean and maximal handgrip strength. Muscle fatigability during the second year post showed a negative correlation with threshold recognition after 20 months (Fig. 4). Similarly, poorer recovery capacity was linked to lower odor identification (Fig. 4). These associations were not observed in PCS patients. Age showed a negative correlation with odor identification across all participants during the second and third year post-infection but was not associated with other olfactory outcomes (Fig. 4). Sex was

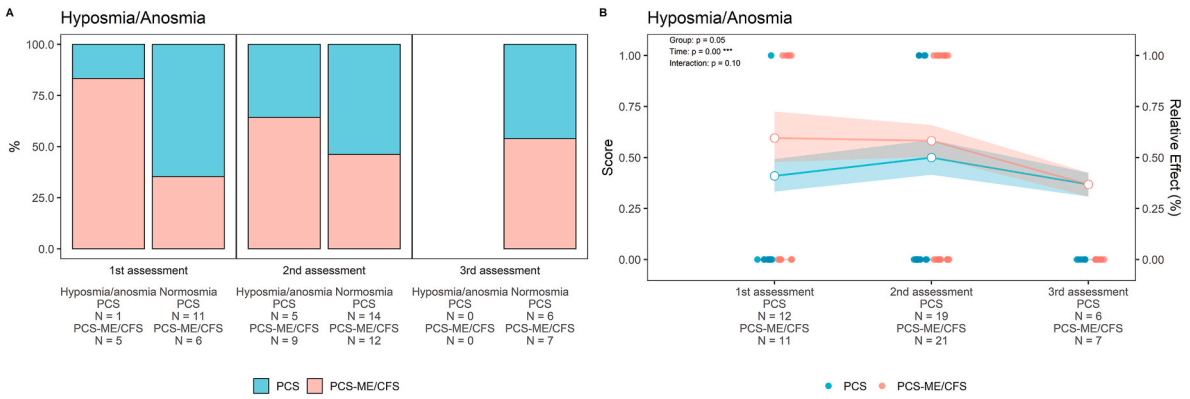

Fig. 2. Longitudinal Assessment of Hyposmia/Anosmia in PCS and PCS-ME/CFS Over Three Timepoints. (A) Percentage of PCS (blue) and PCS-ME/CFS (red) patients (depicted on the y-axis) categorized by normosmia (left bar) and hyposmia/anosmia (right bar), with absolute patient numbers per diagnosis group (shown on the x-axis). Assessment periods are indicated on the x-axis. (B) Hyposmia/anosmia as defined by the TDI Test total score, with a value of 1 representing hyposmia/anosmia and a value of 0 representing normosmia (left y-axis). Blue dots represent PCS patients; red dots represent PCS-ME/CFS patients. Bars show group medians. Lines (blue for PCS, red for PCS-ME/CFS) represent the change in relative effects over three timepoints as quantified on the right y-axis, with the colored surfaces indicating their 95 % confidence intervals. Assessment periods and absolute participant numbers per diagnosis group are indicated on the x-axis. $p \leq 0.05 = *$, $p \leq 0.01 = **$, $p \leq 0.001 = ***$.
Abbreviations: post-COVID syndrome (PCS), post-COVID syndrome fulfilling criteria of myalgic encephalomyelitis/chronic fatigue syndrome (PCS-ME/CFS), Threshold-Discrimination-Identification Test (TDI).

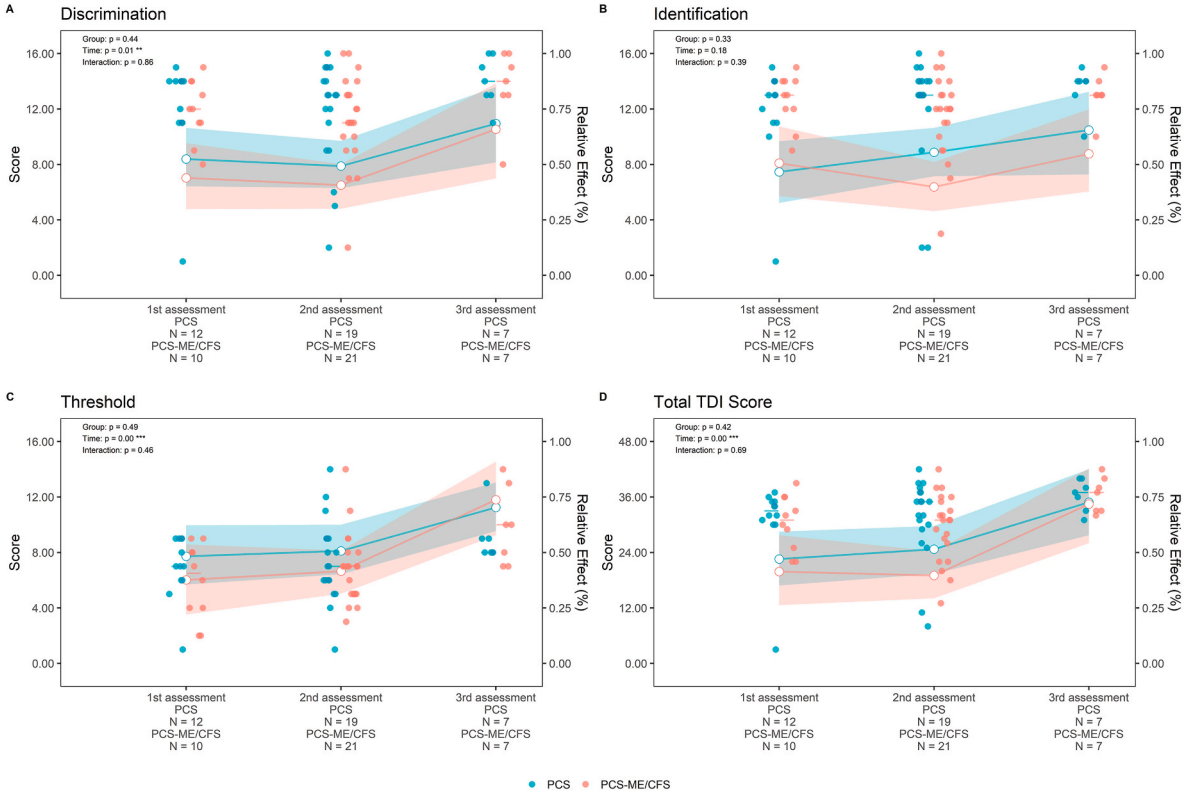

Fig. 3. Longitudinal Assessment of Olfactory Function in PCS and PCS-ME/CFS Over Three Timepoints. (A) Discrimination, (B) Identification, (C) Threshold, and (D) Total TDI Score as defined by the TDI test, with absolute test scores on the left y-axis. Blue dots represent PCS patients, red dots represent PCS-ME/CFS patients, as shown on the color legends below the plots. Bars show group medians. Lines (blue for PCS, red for PCS-ME/CFS) represent the change in relative effects over three timepoints as quantified on the right y-axis, with the colored surfaces indicating their 95 % confidence intervals. Assessment periods and absolute participant numbers per diagnosis group are indicated on the x-axis. $p \leq 0.05 = *$, $p \leq 0.01 = **$, $p \leq 0.001 = ***$.
Abbreviations: post-COVID syndrome (PCS), post-COVID syndrome fulfilling criteria of myalgic encephalomyelitis/chronic fatigue syndrome (PCS-ME/CFS), Threshold-Discrimination-Identification Test (TDI).

not linked to olfactory performance (Fig. 4).

Quite astonishingly, in the PCS-ME/CFS group, more severe fatigue (measured by the CFQ) was linked to a lower frequency of hyposmia/anosmia and better odor threshold results early in the disease, as well as improved odor identification more than 20 months after infection. At the same time, better early olfactory performances were associated with improved emotional role functioning-related quality of life (SF-36) despite reduced daily functioning (Bell Score; Fig. 5). Cognitive

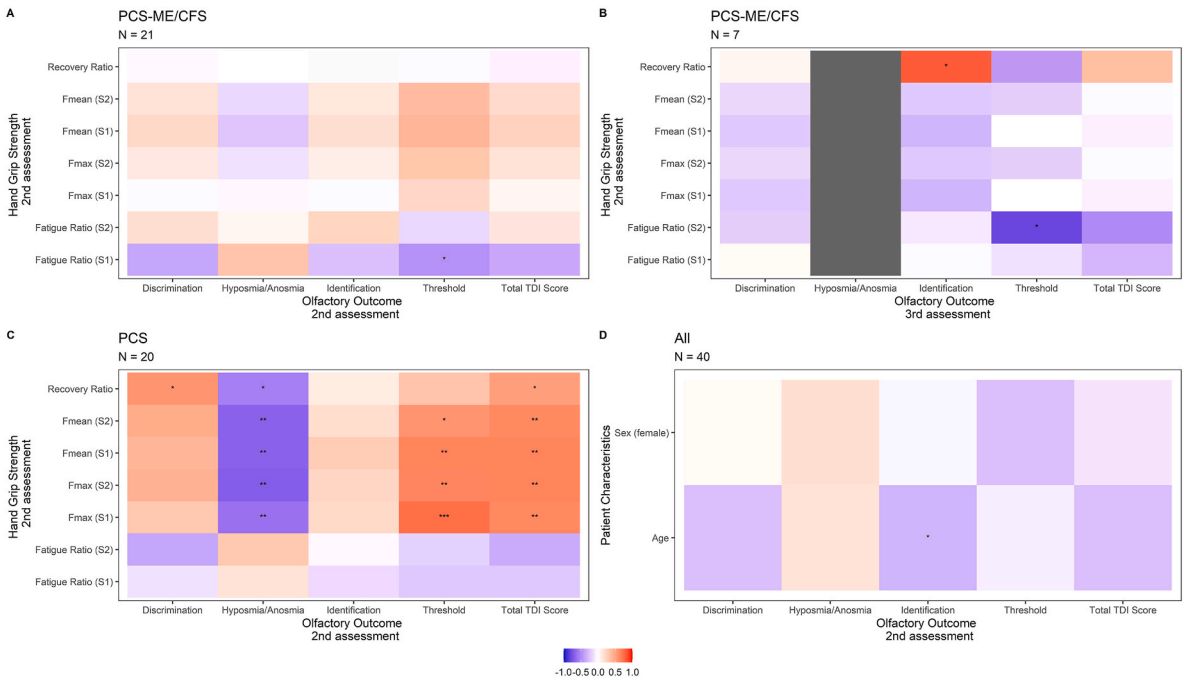

Fig. 4. Correlation of Olfactory Function with Physical Performance in (A), (B) PCS-ME/CFS Patients, (C) PCS Patients, and (D) All Patients. The respective assessment period is indicated on both axes of the heatmaps. Olfactory testing outcomes (including the TDI test scores Discrimination, Identification, Threshold, Total Score, along with Hyposmia/Anosmia classification [yes/no]) are depicted on the x-axis, and HGS markers as a proxy of physical performance on the y-axis. Color scale below the panels indicates the strength and direction of correlation (blue = negative correlation, red = positive correlation), as shown in the $p \leq 0.05 = *$, $p \leq 0.01 = **$, $p \leq 0.001 = ***$.
Abbreviations: post-COVID syndrome (PCS), post-COVID syndrome fulfilling criteria of myalgic encephalomyelitis/chronic fatigue syndrome (PCS-ME/CFS), hand grip strength (HGS).

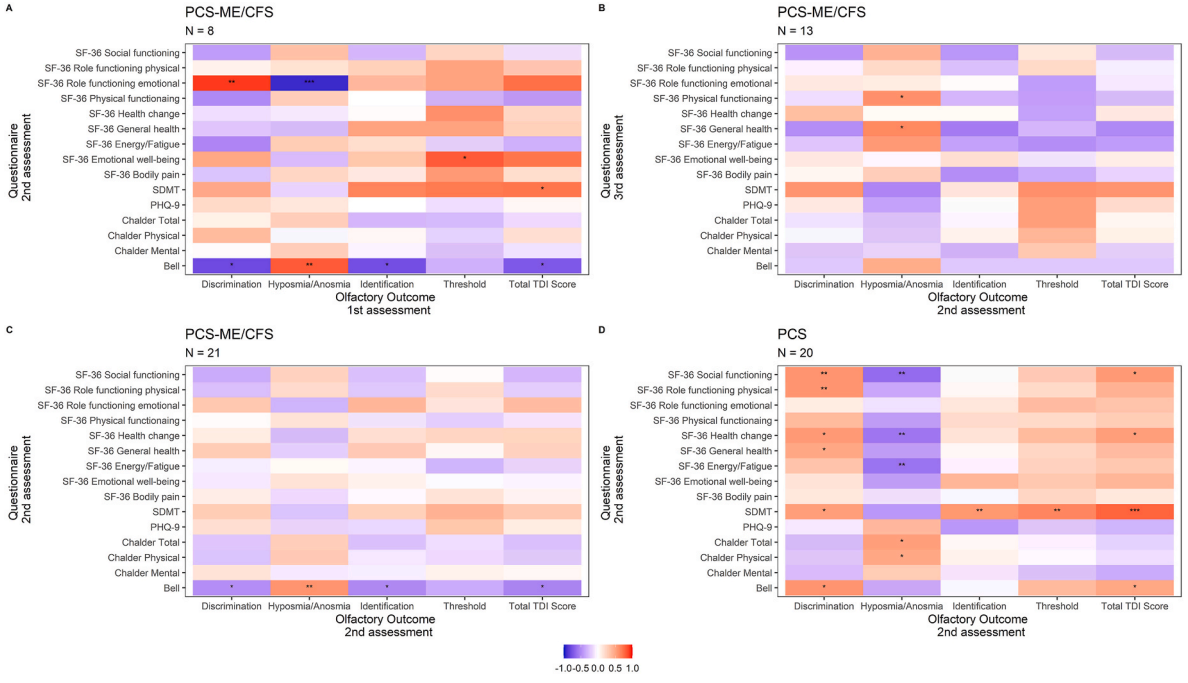

Fig. 5. Correlation of Olfactory Function with Cognitive Performance, Quality of Life and Fatigue in (A), (B), (D) PCS-ME/CFS Patients, and (C) PCS Patients. The respective assessment period is indicated on both axes of the heatmaps. Olfactory testing outcomes (including the TDI test scores Discrimination, Identification, Threshold, Total Score, along with Hyposmia/Anosmia classification (yes/no)) are depicted on the x-axis, and clinical outcome measures on the y-axis. Color scale below the panels indicates the strength and direction of correlation (blue = negative correlation, red = positive correlation), as shown in the color legend below the maps. $p \leq 0.05 = *$, $p \leq 0.01 = **$, $p \leq 0.001 = ***$.
Abbreviations: post-COVID syndrome (PCS), post-COVID syndrome fulfilling criteria of myalgic encephalomyelitis/chronic fatigue syndrome (PCS-ME/CFS).

performance (measured by the SDMT) was positively correlated with early olfactory function: Higher total olfactory scores during the first assessment were linked to better cognitive outcomes at the second assessment (and at a trend level at the third).

In the PCS group, similar positive associations were even more pronounced (Fig. 5). Better olfactory outcomes 10 and 20 months post-COVID-19 were associated with improved cognitive performance (SDMT), daily functioning (Bell Score), and various domains of the HRQoL (SF-36; Fig. 5). These associations persisted into the later assessment period. The strongest (positive) correlation - observed only in PCS patients - was identified between early odor discrimination and daily functioning (Bell Score), and physical role functioning- and health change-related quality of life (HRQoL) after 20 months. In this group, lower fatigue levels (CFQ) were also linked to better olfactory outcomes in the second and third year post-infection, particularly in odor discrimination (Fig. 5).

4. Discussion

This study evaluated olfactory impairment in patients experiencing moderate to severe fatigue following an infection with SARS-CoV-2.

Previous studies have indicated that recovery from olfactory dysfunction can continue for two years after viral upper respiratory infection (Boscolo-Rizzo et al., 2023; Liu et al., 2023). Our study group has recently demonstrated that patients with PCS who fulfill the diagnostic criteria for ME/CFS tend to experience more severe and persistent functional impairment compared to those who are not diagnosed with ME/CFS (Legler et al., 2023). This led us to explore the impact of post-COVID fatigue syndromes on olfactory function.

To assess olfactory impairment comprehensively, we employed the extended Sniffin' Sticks test, a 3-stage evaluation of smell function that provides an understanding of potential underlying mechanisms of olfactory dysfunction. Notably, self-reported assessments of olfactory ability are often unreliable, making standardized tests essential for accurate outcomes (Philpott et al., 2006). The threshold score primarily reflects peripheral olfactory function, involving the detection of odorants by olfactory sensory neurons in the nasal epithelium through G-protein coupled odorant receptors and signal transmission via the olfactory nerve to the olfactory bulb. In contrast, odor identification and discrimination assess central processing, which involves higher-order brain regions (i.e., the olfactory cortex), such as the piriform cortex, orbitofrontal cortex, hippocampus, and other temporal lobe structures. These central processes are responsible for the interpretation, differentiation, memorizing, and semantic recognition of odors - functions that are often impaired in neurodegenerative diseases (Fatuzzo et al., 2023; Hummel et al., 2016).

In our study, patients were evaluated up to 28 months post infection. While several studies suggest (Boscolo-Rizzo et al., 2023; Lechien et al., 2023; Santos et al., 2021) that olfactory ability can fluctuate and change within two years following infection, our current data did not reveal significant changes in olfactory function over a 20-month period. We found that olfactory threshold detection was the most compromised parameter following COVID-19 infection, which aligns with findings from other studies (Boscolo-Rizzo et al., 2021, 2023). Initially, threshold scores were low but improved across all patients starting around 20 months post-COVID-19. This mirrors the overall improvement in olfactory function: although changes were not significant within the first 20 months post-infection, both patient groups demonstrated significant improvements in overall olfactory function, olfactory threshold and odor discrimination scores after 20 months. By this time, all analyzed patients had returned to a normosmic state. In contrast, odor identification was the only olfactory measure that did not show significant improvement. In the PCS-ME/CFS group, odor identification initially declined during the first 20 months before returning to the initial levels, while the PCS group showed a more continuous improvement. This pattern may reflect central processing difficulties in the PCS-ME/CFS group during the early months post-infection. Also, higher age was associated with reduced odor identification. Age-related decline in olfactory performance is a well-known physiological process. A larger cohort study is warranted to evaluate olfactory function in PCS patients in an age-stratified manner.

The SARS-CoV-2 variant appears to influence the severity and persistence of olfactory impairment. Specifically, the wildtype and Alpha variants have been associated with more pronounced and enduring dysfunction compared to the Omicron variant (Sharetts et al., 2024). Our data seem to support this, but the unequal distribution of variants in our sample limits definite conclusions. Additionally, all patients vaccinated prior to SARS-CoV-2 infection were in the group infected with a later variant, and PCS patients were more frequently infected with later variants, which may partly explain their better olfactory outcomes.

It remains unclear whether vaccination against SARS-CoV-2 directly impacts olfactory performance. Some studies suggest a protective effect on other PCS symptoms (Alhazmi et al., 2023), and by reducing the risk of infection, vaccination may indirectly prevent olfactory impairment (Alhazmi et al., 2023). However, there is no evidence that vaccination reverses existing smell impairment. Although rare, temporary smell and taste disturbances have been reported following SARS-CoV-2 vaccination (Konstantinidis et al., 2021) but these appear significantly less common than with other vaccines (Gallagher et al., 2024). In our cohort, only two PCS-ME/CFS patients and three PCS patients were vaccinated before their first SARS-CoV-2 infection, while 10 PCS-ME/CFS patients and 12 PCS patients were vaccinated after their first SARS-CoV-2 infection but before their first study assessment. Given the small sample size of these subgroups, the findings should interpreted with caution. While our data are primarily observational and limited in statistical power, they align with findings from other studies suggesting a protective effect of vaccination on olfactory performance, even when administered during the early months after acute COVID-19. This effect may be related to a strengthened tissue-resident immune response (Alhazmi et al., 2023).

Azcue et al. examined associations between olfactory testing results and various cognitive domains, including general cognition, visual processing speed, verbal and visual memory, attentional capacity and visuospatial ability, in PCS and ME/CFS patients (Azcue et al., 2022). Their findings suggest that prolonged hyposmia may serve as an indicator of cognitive deterioration in PCS patients. However, some limitations of their study warrant consideration. First, they relied solely on an odor identification test, which, in our own data, was the only subtest that did not significantly improve within 20 months post-infection, while all other subtests improved. More importantly, their study lacked an ENT examination to exclude sinonasal pathologies that could contribute to olfactory impairment. Furthermore, they – in contrast to our investigation - did not assess or inquire about participants' olfactory abilities prior to their SARS-CoV-2 infection, which is a significant oversight, as smell impairment is not uncommon even in healthy individuals.

Improved handgrip strength and reduced muscle fatigability in later assessments of the PCS-ME/CFS cohort were linked to better olfactory function during the early post-infection period, suggesting a potential shared underlying mechanism between olfactory performance and muscle fatigue in PCS-ME/CFS. This is consistent with previous findings showing that greater muscle strength is linked to improved olfactory function (Namiranian et al., 2024; Ramírez-Vélez et al., 2021). In line with Azure et al. (Azcue et al., 2022), we also observed a positive correlation in PCS patients between olfactory ability and performance on the SDMT, a measure of cognitive processing speed and attention. This association may reflect overlapping neural circuits involved in both olfaction and cognition, including the orbitofrontal cortex, hippocampus, and other limbic structures (Jacobson et al., 2024; Kostka and Bitzenhofer, 2022). Previous neuroimaging studies found that muscle fatigue is accompanied by reduced activation of the prefrontal cortex as

well as subcortical areas such as thalamus and basal ganglia (Hou et al., 2016; Shortz et al., 2015). These areas are also involved in cognitive control and sensory integration (Zikopoulos and Barbas, 2007), potentially explaining the observed relationships between muscle fatigability, cognitive slowing, and olfactory performance. Furthermore, olfactory dysfunction is increasingly recognized as an early indicator of central nervous system involvement and neuroinflammation, which may also contribute to cognitive impairment in patients with PCS (Fatuzzo et al., 2023). Interestingly, in our study, we found that greater (cognitive) fatigue during the early post-infection period was associated with better olfactory function in PCS-ME/CFS patients. However, this association reversed in the PCS group during later assessments. While these exploratory analyses should be interpreted with caution, this observed shift may indicate that fatigue and olfactory functions follow distinct trajectories and may become functionally independent in more severe forms of PCS, specifically PCS-ME/CFS. The strong association in the PCS only group between odor discrimination ability at the beginning and quality of life and daily functioning after 20 months may serve as a diagnostic tool in this patient group and should be evaluated in larger studies.

The biological mechanisms underlying long-term olfactory dysfunction in PCS patients are still not fully understood. During acute SARS-CoV-2 infection, sustentacular cells in the olfactory epithelium are particularly vulnerable, leading to local inflammation and disruption of the mucosal environment. This often results in transient peripheral olfactory deficits (Kim et al., 2024; Suzuki et al., 2007) detectable via threshold testing. However, sustained impairment may stem from a reduction in olfactory receptor neurons and changes in the olfactory bulb (Chang et al., 2024; Lee et al., 2021), a site increasingly recognized for its susceptibility to viral neuroinvasion and neuroinflammation. In addition, MRI studies have shown structural alterations in central olfactory and limbic regions, including the orbitofrontal cortex, insula, hippocampus, and olfactory cortex (Bitter et al., 2010; Douaud et al., 2022). These areas are highly interconnected with neural networks critical for memory, attention, and executive functions, supporting a neuroanatomical basis for the observed association between cognitive and olfactory deficits (Azcue et al., 2024). Recent studies in PCS patients have further linked reduced olfactory performance with decreased functional connectivity and diminished global network modularity, correlating the latter one with impaired visuospatial memory and executive function (Campabadal et al., 2023; Esposito et al., 2022; Muccioli et al., 2023). Additionally, lower TDI scores have been associated with increased fatigue, poorer emotional well-being, and reduced social functioning (Pendolino et al., 2023). While the reversibility of these changes and their contribution to persistent deficits remain unclear, interventions such as olfactory training have shown both cognitive benefits and neuroplastic changes in relevant brain regions (Vance et al., 2024). The heterogeneity in olfactory recovery post-SARS-CoV-2 infection suggests overlapping pathomechanisms, including persistent neuroinflammation, which may also contribute to chronic fatigue symptoms (Shahbaz et al., 2025). Given prior evidence of co-occurring olfactory dysfunction, cognitive impairment, and fatigue in PCS, we specifically investigated olfaction in a subgroup of patients with pronounced fatigue and neurocognitive symptoms.

A key strength of this study is the comprehensive data collection and detailed clinical characterization of participants, including thorough ENT examinations to exclude alternative causes for olfactory impairment. Certain limitations merit consideration, most notably, the lack of baseline olfactory assessments prior to or during acute COVID-19. Additionally, as this is a real-word observational study, incomplete data across the three study visits per participant, along with the unequal distributions of vaccination status and virus variants, further complicate statistical analyses. Due to the relatively small overall sample size, reliable subgroup analyses were not feasible. Furthermore, given the exploratory nature of the analyses and the broad range of parameters examined, we did not apply corrections for multiple comparisons.

In summary, our findings suggest that improvements in olfactory performance occur only after 20 months following COVID-19, regardless of whether PCS patients meet the full diagnostic criteria for ME/CFS. Notably, odor identification did not improve within the 28 months study period, indicating that central processing may remain impaired. Consistently, our exploratory correlation analyses suggest that early improvements in olfactory function may be linked to better long-term cognitive outcomes, highlighting a potential prognostic role of olfactory function in these patients. These finding warrant validation and further investigation in larger multicenter studies.

CRediT authorship contribution statement

Lil Meyer-Arndt: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Greta Pierchalla:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis. **Lukas Mödl:** Writing – review & editing, Formal analysis. **Felix Wohlrab:** Writing – review & editing, Investigation. **Franziska Legler:** Writing - review & editing, Writing - original draft, Data curation, Investigation. **Uta Hoppmann:** Writing – review & editing, Data curation. **Claudia Kedor:** Writing – review & editing, Data curation. **Kirsten Wittke:** Writing – review & editing, Data curation. **Helma Freitag:** Writing – review & editing, Data curation. **Frank Konietschke:** Writing – review & editing, Resources. **Heidi Olze:** Writing – review & editing, Resources. **Friedemann Paul:** Writing – review & editing, Resources. **Carmen Scheibenbogen:** Writing – review & editing, Resources, Funding acquisition. **Judith Bellmann-Strobl:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Ulrike Förster-Ruhrmann:** Writing – review & editing, Supervision, Methodology.

Data availability statement

The data for this manuscript are available upon reasonable request to the author.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101124.

Abbreviations

BSIT	Brief Smell Identification Test
CCC	Canadian Consensus Criteria
CFQ	Chalder Fatigue Questionnaire
HGS	Hand grip strength
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
PCS	Post-COVID19 syndrome
PEM	Post-exertional malaise
PHQ-9	Patient Health Questionnaire 9
SDMT	Symbol Digit Modality Test
SF-36	Short Form-36
TDI	Threshold-Discrimination-Identification

References

Alhazmi, A., Darraj, H., Aqeel, A., Khormi, G., Hakami, A., Kariri, A., Siddiq, A., Sahli, A., Othathi, R., Sumaily, I., 2023. Effect of vaccination on coronavirus disease 2019-Related olfactory dysfunction. Saudi J. Otorhinolaryngol. Head Neck Surg. 25, 1–6. https://doi.org/10.4103/sjoh.sjoh_58_22.

Azcue, N., Del Pino, R., Saenz de Argandoña, O., Ortiz de Echevarría, A., Acera, M., Fernández-Valle, T., Ayo-Mentxakatorre, N., Lafuente, J.V., Ruiz-Lopez, M., López de Munain, A., Gabilondo, I., Gómez-Esteban, J.C., Tijero-Merino, B., 2024. Understanding the olfactory role in post-COVID cognitive and neuropsychiatric manifestations. Front. Psychol. 15, 1407887. https://doi.org/10.3389/fpsyg.2024.1407887.

Azcue, N., Gómez-Esteban, J.C., Acera, M., Tijero, B., Fernandez, T., Ayo-Mentxakatorre, N., Pérez-Concha, T., Murueta-Goyena, A., Lafuente, J.V., Prada, Á., López de Munain, A., Ruiz-Irastorza, G., Ribacoba, L., Gabilondo, I., Del Pino, R., 2022. Brain fog of post-COVID-19 condition and chronic fatigue syndrome, same medical disorder? J. Transl. Med. 20, 569. https://doi.org/10.1186/s12967-022-03764-2.

Ballering, A.V., van Zon, S.K.R., Olde Hartman, T.C., Rosmalen, J.G.M., Lifelines Corona Research Initiative, 2022. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet Lond. Engl. 400, 452–461. https://doi.org/10.1016/S0140-6736(22)01214-4.

Bell, D.S., 1995. The Doctor's Guide to Chronic Fatigue Syndrome: Understanding, Treating, and Living with CFIDS. Addison-Wesley Pub. Co., Reading, Mass.

Bitter, T., Gudziol, H., Burmeister, H.P., Mentzel, H.J., Guntinas-Lichius, O., Gaser, C., 2010. Anosmia leads to a loss of gray matter in cortical brain areas. Chem. Senses 35, 407–415. https://doi.org/10.1093/chemse/bjq028.

Boscolo-Rizzo, P., Hummel, T., Hopkins, C., Dibattista, M., Menini, A., Spinato, G., Fabbris, C., Emanuelli, E., D'Alessandro, A., Marzolino, R., Zanelli, E., Cancellieri, E., Cargnelutti, K., Fadda, S., Borsetto, D., Vaira, L.A., Gardenal, N., Polesel, J., Tirelli, G., 2021. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. Rhinol. J. https://doi.org/10.4193/Rhin21.249, 0, 0–0.

Boscolo-Rizzo, P., Hummel, T., Invitto, S., Spinato, G., Tomasoni, M., Emanuelli, E., Tofanelli, M., Cavicchia, A., Grill, V., Vaira, L.A., Lechien, J.R., Borsetto, D., Polesel, J., Dibattista, M., Menini, A., Hopkins, C., Tirelli, G., 2023. Psychophysical assessment of olfactory and gustatory function in post-mild COVID-19 patients: a matched case-control study with 2-year follow-up. Int. Forum. Allergy Rhinol. 13, 1864–1875. https://doi.org/10.1002/alr.23148.

Campabadal, A., Oltra, J., Junqué, C., Guillen, N., Botí, M.Á., Sala-Llonch, R., Monté-Rubio, G.C., Lledó, G., Bargalló, N., Rami, L., Sánchez-Valle, R., Segura, B., 2023. Structural brain changes in post-acute COVID-19 patients with persistent olfactory dysfunction. Ann. Clin. Transl. Neurol. 10, 195–203. https://doi.org/10.1002/acn3.51710.

Chang, K., Zaikos, T., Kilner-Pontone, N., Ho, C., 2024. Mechanisms of COVID-19-associated olfactory dysfunction. Neuropathol. Appl. Neurobiol. 50, e12960. https://doi.org/10.1111/nan.12960.

Cristillo, V., Pilotto, A., Cotti Piccinelli, S., Zoppi, N., Bonzi, G., Gipponi, S., Sattin, D., Schiavolin, S., Raggi, A., Bezzi, M., Leonardi, M., Padovani, A., the Neuro Covid Next Study Group, 2021. Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID -19 infection. J. Am. Geriatr. Soc. 69, 2778–2780. https://doi.org/10.1111/jgs.17296.

Damm, M., Temmel, A., Welge-Lüssen, A., Eckel, H.E., Kreft, M.-P., Klussmann, J.P., Gudziol, H., Hüttenbrink, K.-B., Hummel, T., 2004. [Olfactory dysfunctions. Epidemiology and therapy in Germany, Austria and Switzerland]. HNO 52, 112–120. https://doi.org/10.1007/s00106-003-0877-z.

Davis, H.E., McCorkell, L., Vogel, J.M., Topol, E.J., 2023. Author correction: long COVID: major findings, mechanisms and recommendations. Nat. Rev. Microbiol. 21, 408. https://doi.org/10.1038/s41579-023-00896-0.

Devanand, D.P., Lee, S., Manly, J., Andrews, H., Schupf, N., Masurkar, A., Stern, Y., Mayeux, R., Doty, R.L., 2015. Olfactory identification deficits and increased mortality in the community. Ann. Neurol. 78, 401–411. https://doi.org/10.1002/ana.24447.

Di Stadio, A., Brenner, M.J., De Luca, P., Albanese, M., D'Ascanio, L., Ralli, M., Roccamatisi, D., Cingolani, C., Vitelli, F., Camaioni, A., Di Girolamo, S., Bernitsas, E., 2022. Olfactory dysfunction, headache, and mental clouding in adults with Long-COVID-19: what is the link between cognition and olfaction? A cross-sectional study. Brain Sci. 12, 154. https://doi.org/10.3390/brainsci12020154.

Dias, M., Shaida, Z., Haloob, N., Hopkins, C., 2024. Recovery rates and long-term olfactory dysfunction following COVID-19 infection. World J. Otorhinolaryngol. Head Neck Surg. 10, 121–128. https://doi.org/10.1002/wjo2.163.

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J.L.R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A.M., Collins, R., Matthews, P.M., Allen, N., Miller, K.L., Nichols, T.E., Smith, S.M., 2022. SARS-CoV-2 is associated with changes in brain structure in UK biobank. Nature 604, 697–707. https://doi.org/10.1038/s41586-022-04569-5.

Emma, B. Hodcroft, 2021. CoVariants: SARS-coV-2 mutations and variants of interest. https://covariants.org/. August 2024.

Esposito, F., Cirillo, M., De Micco, R., Caiazzo, G., Siciliano, M., Russo, A.G., Monari, C., Coppola, N., Tedeschi, G., Tessitore, A., 2022. Olfactory loss and brain connectivity after COVID -19. Hum. Brain Mapp. 43, 1548–1560. https://doi.org/10.1002/hbm.25741.

Fatuzzo, I., Niccolini, G.F., Zoccali, F., Cavalcanti, L., Bellizzi, M.G., Riccardi, G., de Vincentiis, M., Fiore, M., Petrella, C., Minni, A., Barbato, C., 2023. Neurons, nose, and neurodegenerative diseases: olfactory function and cognitive impairment. Int. J. Mol. Sci. 24, 2117. https://doi.org/10.3390/ijms24032117.

Fokkens, W.J., Lund, V.J., Hopkins, C., Hellings, P.W., Kern, R., Reitsma, S., Toppila-Salmi, S., Bernal-Sprekelsen, M., Mullol, J., Alobid, I., Terezinha Anselmo-Lima, W., Bachert, C., Baroody, F., von Buchwald, C., Cervin, A., Cohen, N., Constantinidis, J., De Gabory, L., Desrosiers, M., Diamant, Z., Douglas, R.G., Gevaert, P.H., Hafner, A., Harvey, R.J., Joos, G.F., Kalogjera, L., Knill, A., Kocks, J.H., Landis, B.N., Limpens, J., Lebeer, S., Lourenco, O., Meco, C., Matricardi, P.M., O'Mahony, L., Philpott, C.M., Ryan, D., Schlosser, R., Senior, B., Smith, T.L., Teeling, T., Tomazic, P.V., Wang, D.Y., Wang, D., Zhang, L., Agius, A.M., Ahlstrom-Emanuelsson, C., Alabri, R., Albu, S., Alhabash, S., Aleksic, A., Aloulah, M., Al-Qudah, M., Alsaleh, S., Baban, M.A., Baudoin, T., Balvers, T., Battaglia, P., Bedoya, J. D., Beule, A., Bofares, K.M., Braverman, I., Brozek-Madry, E., Richard, B., Callejas, C., Carrie, S., Caulley, L., Chussi, D., de Corso, E., Coste, A., El Hadi, U., Elfarouk, A., Eloy, P.H., Farrokhi, S., Felisati, G., Ferrari, M.D., Fishchuk, R., Grayson, W., Goncalves, P.M., Grdinic, B., Grgic, V., Hamizan, A.W., Heinichen, J.V., Husain, S., Ping, T.I., Ivaska, J., Jakimovska, F., Jovancevic, L., Kakande, E., Kamel, R., Karpischenko, S., Kariyawasam, H.H., Kawauchi, H., Kjeldsen, A., Klimek, L., Krzeski, A., Kopacheva Barsova, G., Kim, S.W., Lal, D., Letort, J.J., Lopatin, A., Mahdjoubi, A., Mesbahi, A., Netkovski, J., Nyenbue Tshipukane, D., Obando-Valverde, A., Okano, M., Onerci, M., Ong, Y.K., Orlandi, R., Otori, N., Ouennoughy, K., Ozkan, M., Peric, A., Plzak, J., Prokopakis, E., Prepageran, N., Psaltis, A., Pugin, B., Raftopulos, M., Rombaux, P., Riechelmann, H., Sahtout, S., Sarafoleanu, C.-C., Searyoh, K., Rhee, C.-S., Shi, J., Shkoukani, M., Shukuryan, A.K., Sicak, M., Smyth, D., Sindvongs, K., Soklic Kosak, T., Stjarne, P., Sutikno, B., Steinsvag, S., Tantilipikorn, P., Thanaviratananich, S., Tran, T., Urbancic, J., Valiulius, A., Vasquez de Aparicio, C., Vicheva, D., Virkkula, P.M., Vicente, G., Voegels, R., Wagenmann, M.M., Wardani, R.S., Welge-Lussen, A., Witterick, I., Wright, E., Zabolotniy, D., Zsolt, B., Zwetsloot, C.P., 2020. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 58, 1–464. https://doi.org/10.4193/Rhin20.600.

Gallagher, T.J., Parikh, M., Herrera, K., Lin, M.E., Hur, K., 2024. Association of COVID-19 vaccination with changes in smell and taste. Otolaryngol. Neck Surg. 171, 1240–1244. https://doi.org/10.1002/ohn.833.

Gräfe, K., Zipfel, S., Herzog, W., Löwe, B., 2004. Screening psychischer Störungen mit dem "Gesundheitsfragebogen für Patienten (PHQ-D). Diagnostica 50, 171–181. https://doi.org/10.1026/0012-1924.50.4.171.

Hou, L.J., Song, Z., Pan, Z.J., Cheng, J.L., Yu, Y., Wang, J., 2016. Decreased activation of subcortical brain areas in the motor fatigue state: an fMRI study. Front. Psychol. 7. https://doi.org/10.3389/fpsyg.2016.01154.

Hummel, T., Kobal, G., Gudziol, H., Mackay-Sim, A., 2007. 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. Oto-Rhino-Laryngol. Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. EUFOS Affil. Ger. Soc. Oto-Rhino-Laryngol. - Head Neck Surg. 264, 237–243. https://doi.org/10.1007/s00405-006-0173-0.

Hummel, T., Sekinger, B., Wolf, S.R., Pauli, E., Kobal, G., 1997. "Sniffin" sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem. Senses 22, 39–52. https://doi.org/10.1093/chemse/22.1.39.

Hummel, T., Whitcroft, K.L., Andrews, P., Altundag, A., Cinghi, C., Costanzo, R.M., Damm, M., Frasnelli, J., Gudziol, H., Gupta, N., Haehner, A., Holbrook, E., Hong, S. C., Hornung, D., Hüttenbrink, K.B., Kamel, R., Kobayashi, M., Konstantinidis, I., Landis, B.N., Leopold, D.A., Macchi, A., Miwa, T., Moesges, R., Mullol, J., Mueller, C. A., Ottaviano, G., Passali, G.C., Philpott, C., Pinto, J.M., Ramakrishnan, V.J., Rombaux, P., Roth, Y., Schlosser, R.A., Shu, B., Soler, G., Stjärne, P., Stuck, B.A., Vodicka, J., Welge-Luessen, A., 2016. Position paper on olfactory dysfunction. Rhinology 56, 1–30. https://doi.org/10.4193/Rhino16.248.

Jacobson, P.T., Vilarello, B.J., Tervo, J.P., Waring, N.A., Gudis, D.A., Goldberg, T.E., Devanand, D.P., Overdevest, J.B., 2024. Associations between olfactory dysfunction and cognition: a scoping review. J. Neurol. 271, 1170–1203. https://doi.org/10.1007/s00415-023-12057-7.

Jäkel, B., Kedor, C., Grabowski, P., Wittke, K., Thiel, S., Scherbakov, N., Doehner, W., Scheibenbogen, C., Freitag, H., 2021. Hand grip strength and fatigability: correlation with clinical parameters and diagnostic suitability in ME/CFS. J. Transl. Med. 19, 159. https://doi.org/10.1186/s12967-021-02774-w.

Jason, L.A., Sunnquist, M., Brown, A., Reed, J., 2015. Defining essential features of myalgic encephalomyelitis and chronic fatigue syndrome. J. Hum. Behav. Soc. Environ. 25, 657–674. https://doi.org/10.1080/10911359.2015.1011256.

Kedor, C., Freitag, H., Meyer-Arndt, L., Wittke, K., Hanitsch, L.G., Zoller, T., Steinbeis, F., Haffke, M., Rudolf, G., Heidecker, B., Bobbert, T., Spranger, J., Volk, H.-D., Skurk, C., Konietschke, F., Paul, F., Behrends, U., Bellmann-Strobl, J., Scheibenbogen, C., 2022. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat. Commun. 13, 5104. https://doi.org/10.1038/s41467-022-32507-6.

Kim, S., Finlay, J.B., Ko, T., Goldstein, B.J., 2024. Long-term olfactory loss post-COVID-19: pathobiology and potential therapeutic strategies. World J. Otorhinolaryngol. Head Neck Surg. 10, 148–155. https://doi.org/10.1002/wjo2.165.

Konstantinidis, I., Tsakiropoulou, E., Hähner, A., De With, K., Poulas, K., Hummel, T., 2021. Olfactory dysfunction after coronavirus disease 2019 (COVID-19) vaccination. Int. Forum Allergy Rhinol. 11, 1399–1401. https://doi.org/10.1002/alr.22809.

Kostka, J.K., Bitzenhofer, S.H., 2022. How the sense of smell influences cognition throughout life. Neuroform 28, 177–185. https://doi.org/10.1515/nf-2022-0007.

Lechien, J.R., Chiesa-Estomba, C.M., Beckers, E., Mustin, V., Ducarme, M., Journe, F., Marchant, A., Jouffe, L., Barillari, M.R., Cammaroto, G., Circiu, M.P., Hans, S., Saussez, S., 2021. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. J. Intern. Med. 290, 451–461. https://doi.org/10.1111/joim.13209.

Lechien, J.R., Vaira, L.A., Saussez, S., 2023. Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: a multicentre prospective study. J. Intern. Med. 293, 82–90. https://doi.org/10.1111/joim.13564.

Lee, M.-H., Perl, D.P., Nair, G., Li, W., Maric, D., Murray, H., Dodd, S.J., Koretsky, A.P., Watts, J.A., Cheung, V., Masliah, E., Horkayne-Szakaly, I., Jones, R., Stram, M.N., Moncur, J., Hefti, M., Folkerth, R.D., Nath, A., 2021. Microvascular injury in the brains of patients with Covid-19. N. Engl. J. Med. 384, 481–483. https://doi.org/10.1056/NEJMc2033369.

Legler, F., Meyer-Arndt, L., Mödl, L., Kedor, C., Freitag, H., Stein, E., Hoppmann, U., Rust, R., Wittke, K., Siebert, N., Behrens, J., Thiel, A., Konietschke, F., Paul, F., Scheibenbogen, C., Bellmann-Strobl, J., 2023. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort. eClinicalMedicine 63, 102146. https://doi.org/10.1016/j.eclinm.2023.102146.

Liu, Z.Y., Vaira, L.A., Boscolo-Rizzo, P., Walker, A., Hopkins, C., 2023. Post-viral olfactory loss and parosmia. BMJ Med 2, e000382. https://doi.org/10.1136/bmjmed-2022-000382.

Llana, T., Mendez, M., Garces-Arilla, S., Hidalgo, V., Mendez-Lopez, M., Juan, M.-C., 2023. Association between olfactory dysfunction and mood disturbances with objective and subjective cognitive deficits in long-COVID. Front. Psychol. 14, 1076743. https://doi.org/10.3389/fpsyg.2023.1076743.

MacDonald, S.W.S., Keller, C.J.C., Brewster, P.W.H., Dixon, R.A., 2018. Contrasting olfaction, vision, and audition as predictors of cognitive change and impairment in non-demented older adults. Neuropsychology 32, 450–460. https://doi.org/10.1037/neu0000439.

Morriss, R., Wearden, A., Mullis, R., 1998. Exploring the validity of the chalder fatigue scale in chronic fatigue syndrome. J. Psychosom. Res. 45, 411–417. https://doi.org/10.1016/S0022-3999(98)00022-1.

Muccioli, L., Sighinolfi, G., Mitolo, M., Ferri, L., Jane Rochat, M., Pensato, U., Taruffi, L., Testa, C., Masullo, M., Cortelli, P., Lodi, R., Liguori, R., Tonon, C., Bisulli, F., 2023. Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction. NeuroImage Clin. 38, 103410. https://doi.org/10.1016/j.nicl.2023.103410.

Namiranian, K., Gauthier, A.-C., Gilbert, J.-A., Mathieu, M.-E., 2024. The association between parameters of physical activity and olfactory function—the importance of frequency and moderate intensity. Front. Sports act. Living 6, 1394858. https://doi.org/10.3389/fspor.2024.1394858.

Noguchi, K., Gel, Y.R., Brunner, E., Konietschke, F., 2012. nparLD : an *R* software package for the nonparametric analysis of longitudinal data in factorial experiments. J. Stat. Software 50. https://doi.org/10.18637/jss.v050.i12.

Pendolino, A.L., Tan, H.Q.M., Choi, D., Ottaviano, G., Andrews, P.J., 2023. Long-term quality-of-life impairment in patients with more than 1-year COVID-19-related olfactory dysfunction. Int. Forum Allergy Rhinol. 13 (2), 160–164. https://doi.org/10.1002/alr.23071, 2023 Feb.

Philpott, C.M., Wolstenholme, C.R., Goodenough, P.C., Clark, A., Murty, G.E., 2006. Comparison of subjective perception with objective measurement of olfaction. Otolaryngol.–Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg. 134, 488–490. https://doi.org/10.1016/j.otohns.2005.10.041.

Ramírez-Vélez, R., López-Gil, J.F., De Asteasu, M.L.S., Izquierdo, M., García-Hermoso, A., 2021. Handgrip strength as a moderator of the influence of age on olfactory impairment in US adult population $\geq$ 40 years of age. Sci. Rep. 11, 14085. https://doi.org/10.1038/s41598-021-93355-w.

Santos, R.E.A., da Silva, M.G., do Monte Silva, M.C.B., Barbosa, D.A.M., Gomes, A.L. do V., Galindo, L.C.M., da Silva Aragão, R., Ferraz-Pereira, K.N., 2021. Onset and duration of symptoms of loss of smell/taste in patients with COVID-19: a systematic review. Am. J. Otolaryngol. 42, 102889. https://doi.org/10.1016/j.amjoto.2020.102889.

Schubert, C.R., Cruickshanks, K.J., Fischer, M.E., Huang, G.-H., Klein, R., Pankratz, N., Zhong, W., Nondahl, D.M., 2013. Odor identification and cognitive function in the beaver dam offspring study. J. Clin. Exp. Neuropsychol. 35, 669–676. https://doi.org/10.1080/13803395.2013.809701.

Shahbaz, S., Rezaeifar, M., Syed, H., Redmond, D., Terveart, J.W.C., Osman, M., Elahi, S., 2025. Upregulation of olfactory receptors and neuronal-associated genes highlights complex immune and neuronal dysregulation in long COVID patients. Brain Behav. Immun. 124, 97–114. https://doi.org/10.1016/j.bbi.2024.11.032.

Sharetts, R., Moein, S.T., Khan, R., Doty, R.L., 2024. Long-term taste and smell outcomes after COVID-19. JAMA Netw. Open 7, e247818. https://doi.org/10.1001/jamanetworkopen.2024.7818.

Shortz, A.E., Pickens, A., Zheng, Q., Mehta, R.K., 2015. The effect of cognitive fatigue on prefrontal cortex correlates of neuromuscular fatigue in older women. J. NeuroEng. Rehabil. 12, 115. https://doi.org/10.1186/s12984-015-0108-3.

Sivan, M., Taylor, S., 2020. NICE guideline on long covid. BMJ 371, m4938. https://doi.org/10.1136/bmj.m4938.

Speth, M.M., Speth, U.S., Sedaghat, A.R., Hummel, T., 2022. [Olfactory and gustatory disorders]. HNO 70, 157–166. https://doi.org/10.1007/s00106-021-01132-y.

Stavem, K., Ghanima, W., Olsen, M.K., Gilboe, H.M., Einvik, G., 2021. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. Int. J. Environ. Res. Publ. Health 18, 2030. https://doi.org/10.3390/ijerph18042030.

Strober, L.B., Bruce, J.M., Arnett, P.A., Alschuler, K.N., Lebkuecher, A., Di Benedetto, M., Cozart, J., Thelen, J., Guty, E., Roman, C., 2020. A new look at an old test: normative data of the symbol digit modalities test –Oral version. Mult. Scler. Relat. Disord. 43, 102154. https://doi.org/10.1016/j.msard.2020.102154.

Suzuki, M., Saito, K., Min, W., Vladau, C., Toida, K., Itoh, H., Murakami, S., 2007. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 117, 272–277. https://doi.org/10.1097/01.mlg.0000249922.37381.1e.

Vance, D.E., Del Bene, V.A., Kamath, V., Frank, J.S., Billings, R., Cho, D.-Y., Byun, J.Y., Jacob, A., Anderson, J.N., Visscher, K., Triebel, K., Martin, K.M., Li, W., Puga, F., Fazeli, P.L., 2024. Does olfactory training improve brain function and cognition? A systematic review. Neuropsychol. Rev. 34, 155–191. https://doi.org/10.1007/s11065-022-09573-0.

Ware, J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30, 473–483.

World Health Organization, 2022. Post COVID-19 condition (long COVID). https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition. August 2023.

Yaffe, K., Freimer, D., Chen, H., Asao, K., Rosso, A., Rubin, S., Tranah, G., Cummings, S., Simonsick, E., 2017. Olfaction and risk of dementia in a biracial cohort of older adults. Neurology 88, 456–462. https://doi.org/10.1212/WNL.0000000000003558.

Yahiaoui-Doktor, M., Luck, T., Riedel-Heller, S.G., Loeffler, M., Wirkner, K., Engel, C., 2019. Olfactory function is associated with cognitive performance: results from the population-based LIFE-Adult-Study. Alzheimers Res. Ther. 11, 43. https://doi.org/10.1186/s13195-019-0494-z.

Zikopoulos, B., Barbas, H., 2007. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in Primates. Rev. Neurosci. 18. https://doi.org/10.1515/REVNEURO.2007.18.6.417.