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COVID-19 related olfactory dysfunction: Neuropsychiatric, psychological, and cognitive effects

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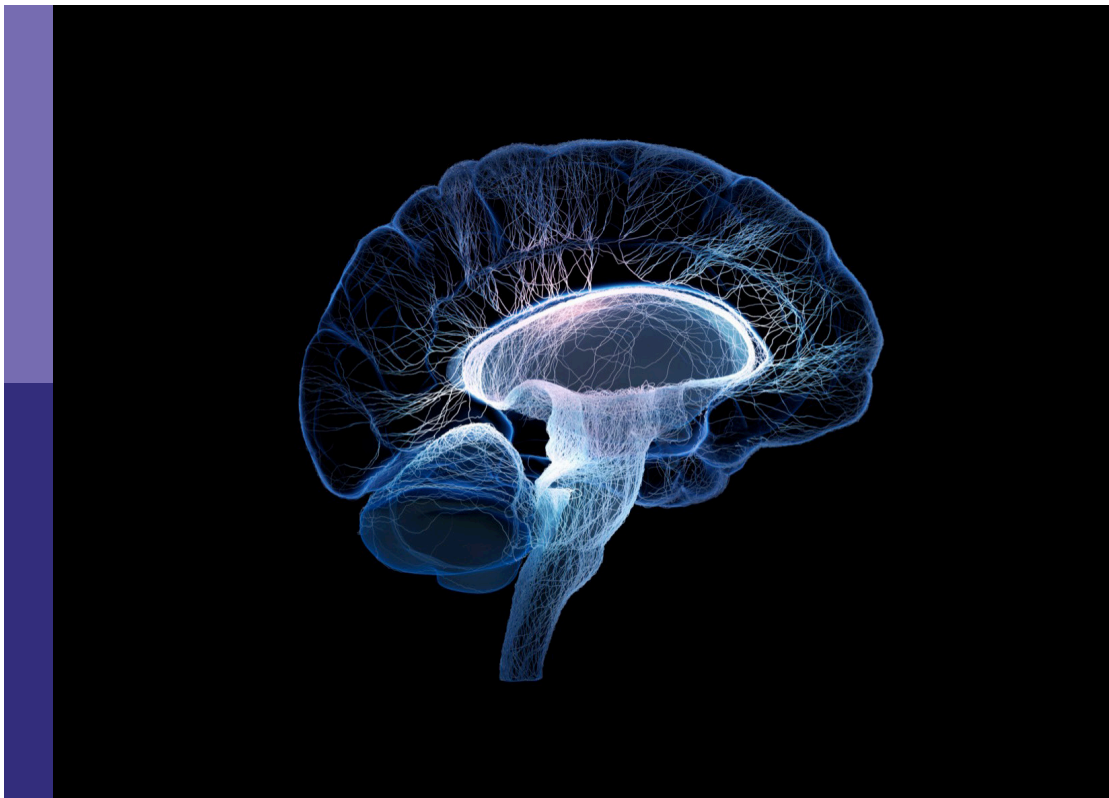

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COVID-19 related olfactory dysfunction: Neuropsychiatric, psychological, and cognitive effects

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Editorial: COVID-19 related olfactory dysfunction: neuropsychiatric, psychological, and cognitive effects

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COVID-19, olfactory dysfunction, affective disorder, cognitive impairment, neuroplasticity

Editorial on the Research Topic
COVID-19 related olfactory dysfunction: neuropsychiatric, psychological, and cognitive effects

Introduction

Olfactory dysfunction (OD), also known as loss of smell and hyposmia, is one of the common symptoms of COVID-19 (corona virus disease 2019), with a reported incidence of up to 80–90% (Cardoso et al., 2022). In addition, there are more than 755 million cumulative cases of COVID-19 worldwide, and millions of patients are currently experiencing olfactory and gustatory deficits (Cecchetto et al., 2021; Ohla et al., 2022). Some patients recover in the short term, but a significant portion of patients still suffer from long-term OD even after 2 years of infection with COVID-19 (McWilliams et al., 2022). Furthermore, OD is associated with disturbances in daily life and interpersonal interactions, which are unfavorable to physical and mental health development (Erskine and Philpott, 2020; Elkholi et al., 2021). Individuals with OD often exhibit depressive and anxious states, self-esteem deficits, diminished intensities of affective experiences, and a reduced quality of life (Glezer et al., 2021; Schäfer et al., 2021). This presents novel challenges, emphasizes, and exacerbates unmet needs for adequate access to health care for those COVID-19 patients suffering from OD (Ball et al., 2021).

The short- and long-term neuropsychiatric consequences, as well as the molecular mechanisms, of COVID-19-related OD have not been well studied. Investigating the neuropsychiatric sequelae of OD associated with COVID-19 infection is particularly important to characterize the pathological effects of COVID-19 on brain function and to develop strategies to improve the quality of life and mental health of patients, which is the focus of this Research Topic.

Within this context, we launched our Research Topic on September 13, 2022, and invited researchers to address the COVID-19 Related Olfactory Dysfunction: Neuropsychiatric, Psychological, and Cognitive Effects both on a personal and a social level. This Research Topic has had the pleasure of receiving diverse and insightful manuscript proposals. Frontiers in Neuroscience published five original articles, four reviews, and one opinion, involving 61 authors from 6 countries, which were contained in Perception Science specialized sections. Based on the objective of each contributed article, we can group them into two major categories, including (1) associations of COVID-19-related OD with neuropsychiatric, psychological, and cognitive consequences; (2) impacts and therapeutic interventions of COVID-19-related OD (Figure 1).

Associations of COVID-19-related OD with neuropsychiatric, psychological, and cognitive consequences

Llana, Mendez, Zorzo, et al. recruited 42 long-COVID patients and 30 controls. Their objective performance in the dissociative memory system, including associated symptoms of OD, was assessed and compared. The results suggest that COVID-19-induced olfactory deficits might be associated with long-term limbic system dysfunction.

In another 6-month cross-sectional study, Llana, Mendez, Garces-Arilla, et al. enrolled 128 long-COVID participants in Spain, which is the first time to identify correlations between OD and subjective and objective memory scores, general cognitive functioning, and mood disorders. These findings will give easy access to a deeper understanding of the neuropsychological and emotional aspects of the long COVID.

Tai et al. provide a mini-review that summarizes the sense of smell and its neural correlates and discusses possible mechanistic pathways for how COVID-19 affects olfactory function and its damage to the central nervous system, leading to neuropsychiatric symptoms.

In an opinion paper, Kocsis and Pittman-Polletta proposed that damaged non-olfactory inputs generated by the olfactory epithelium are intimately related to cognitive function, and respiratory-related oscillations can be a hidden mechanism for the neuropsychiatric sequelae of OD associated with COVID-19 infection.

Additionally, a captivating scoping review summarized the existing literature to assess the association between neurocognition and olfaction among non-agenarians after COVID-19 infection. Vilarello et al. found that patients with OD had significantly worse cognitive performance, providing a bridge to understanding the neural mechanism underlying the relationship between olfaction and cognition after pericoronitis.

Impacts and therapeutic interventions of COVID-19-related OD

Yang et al. used VOSviewer to quantitatively analyze and visualize the current research status and development trend of COVID-19-induced OD retrieved from the Web of Science, and finally identified six research hotspots and revealed that the temporal evolution of COVID-19-related OD can be classified into three phases. These results provide effective assessment and intervention strategies for future related studies.

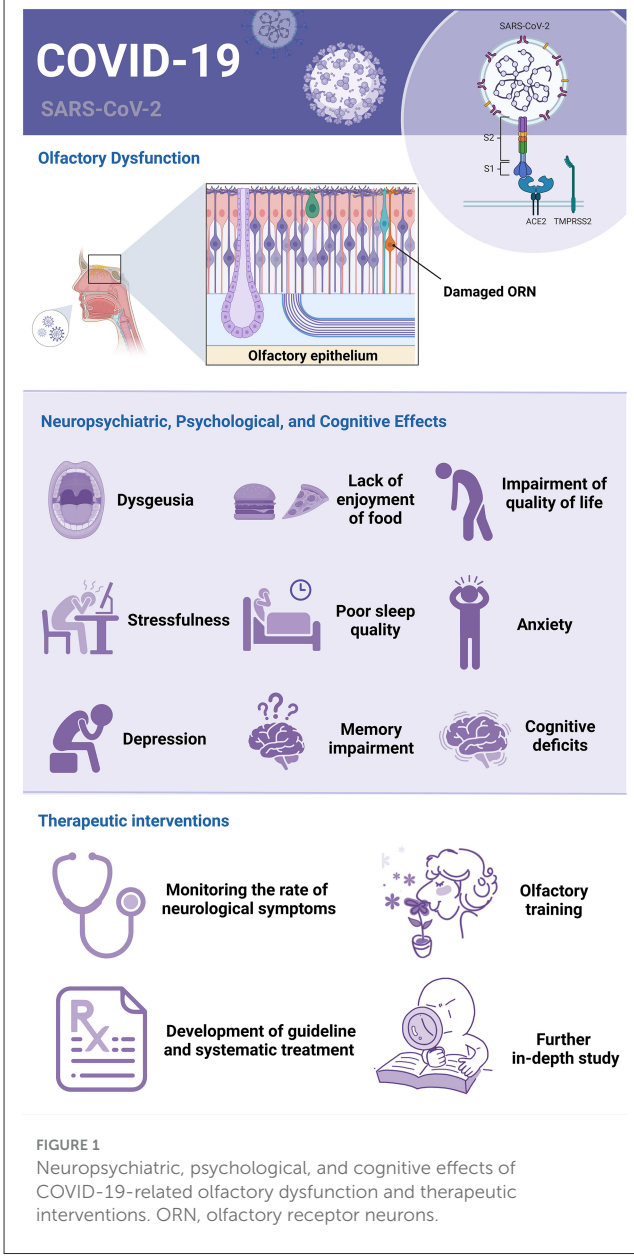

FIGURE 1
Neuropsychiatric, psychological, and cognitive effects of COVID-19-related olfactory dysfunction and therapeutic interventions. ORN, olfactory receptor neurons.

Winter et al. assessed 58 individuals diagnosed with COVID-19 and self-perceived OD using questionnaires and the Sniffin' Sticks extended test battery. The results revealed a positive correlation between qualitative OD and the degree of impairments in daily living. The primary cause of diminished quality of life was the absence of food enjoyment. These outcomes highlight the importance of risk assessment in future clinical studies and the development of new intervention strategies.

A Brazilian cross-sectional survey involved a total of 288 participants with long COVID and self-reported neurological symptoms (anxiety, cognitive impairment, and olfactory

disturbances), which were assessed using standardized self-rating scales by Paranhos et al. Anxiety and olfactory disturbances were identified in a high percentage of patients with poor sleep quality. This study recommended that neurological symptoms associated with COVID-19 should be emphasized and monitored in the long term.

Kumari et al. recruited 15 participants with persistent COVID-19-related olfactory and/or gustatory deficits in the United Kingdom. Through the application of a new Camera-Based Visual Feedback Learning Aid (CVFLA) device, the intervention was found to restore olfactory and gustatory deficits associated with COVID-19. The proof-of-concept study also explored possible mechanisms by which CVFLA improved the sense of smell or taste.

In a comprehensive review, Jegatheeswaran et al. summarized the obvious relationships between long-COVID and psychological, neuropsychiatric, and cognitive symptoms, and provided a guideline and theoretical basis for the evaluation of olfactory disorder, and psychophysical effects in patients with COVID-19.

Overall, the original research and review papers in this Research Topic assemble a range of topics that systematically explore the correlations and possible mechanisms of neuropsychiatric, psychological, and cognitive consequences of COVID-19-related OD, which also present the recent and cutting-edge research on the assessment or prevention of long-COVID-related OD, in addition to new therapeutic strategies. This topic paved the way for future research on virus-induced OD-related diseases. We hope that this Research Topic will go some way toward helping researchers around the world to search for more associations between olfactory disorders and neurological impairments, thus helping to refine our understanding of COVID-19 induced multiple comorbidities. Additionally, this topic will aid in guiding public policy formulation.

Author contributions

YZ: Writing—original draft. XL: Writing—original draft. ZT: Supervision, Writing—review & editing. DQ: Conceptualization, Supervision, Writing—original draft, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Anosmia in COVID-19 could be associated with long-term deficits in the consolidation of procedural and verbal declarative memories

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Background and purpose: Long-COVID describes the long-term effects of the coronavirus disease 2019 (COVID-19). In long-COVID patients, neuropsychological alterations are frequently reported symptoms. Research points to medial temporal lobe dysfunction and its association with anosmia in long-COVID patients. This study aims to investigate the acquisition and consolidation of declarative and procedural memory in long-COVID patients and to explore whether anosmia is related to these dissociated memory functions.

Methods: Forty-two long-COVID participants and 30 controls (C) were recruited. The sample of long-COVID patients was divided into two groups based on the presence or absence of anosmia, group A and group NA, respectively. Objective performance in verbal declarative memory (Paired-Associate Learning, PAL), procedural memory (Mirror Tracing Test, MTT), general cognitive function (Montreal Cognitive Assessment scale), psychomotor speed, and incidental learning (Digit Symbol Substitution Test) were assessed and compared among the A, NA, and C groups. Long-term retention of PAL and MTT were assessed 24 h after acquisition.

Results: Lower scores in general cognition, psychomotor speed, and sustained attention were found in A and NA compared with C. However, incidental learning, both cue-guided and free-recalled, was diminished in group A compared with C, with no differences with group NA. General cognition and incidental learning were related to declarative memory function exclusively in long-COVID groups. Long-COVID groups presented lower long-term retention of verbal declarative memory than controls in recall tests but no differences in recognition tests. No group differences were found

in the acquisition of procedural memory. However, long-term retention of this memory was worse in group A as compared to the NA and C groups, respectively, when errors and time of execution were considered.

Conclusion: Findings support that consolidation of both procedural and declarative memories is more affected than the acquisition of these memories in long-COVID patients, who are also more vulnerable to deficits in delayed recall than in recognition of declarative memories. Deficits in the consolidation of procedural memory and immediate recall of declarative information are especially relevant in long-COVID participants with anosmia. This indicates that anosmia in COVID-19 could be associated with a long-term dysfunction of the limbic system.

KEYWORDS

long-COVID, declarative memory, implicit memory, incidental learning, anosmia

Introduction

Coronavirus disease (COVID-19) is a multisystemic illness caused by the severe acute respiratory syndrome-2 infection (SARS-CoV-2), which can produce various symptoms, including upper respiratory symptoms, fever, and changes in taste and smell as the most common, but also extrapulmonary complications including the cardiovascular, gastrointestinal, dermatological, and neurological systems (Long et al., 2022). The alteration of these systems can last for months in some patients with long-COVID syndrome. This syndrome is described as symptoms that occur beyond 3 months from the onset of COVID-19, last for at least 2 months, and cannot be explained by an alternative diagnosis (World Health Organization [WHO], 2021). The estimated prevalence ratio of persistent symptoms after the infection is 0.54 in hospitalized and 0.34 in non-hospitalized patients, with fatigue, with a prevalence of 0.23, being the most common symptom reported, followed by memory problems with an estimated prevalence of 0.14 (Chen et al., 2022).

Regarding the etiology of long-COVID, studies have not yet reached a definite conclusion, but researchers have drawn hypotheses about the physiological pathways that may lead to the direct consequences of the viral infection in combination with inflammatory or autoimmune responses. Thus, some of the etiological factors for long-term symptoms associated with COVID-19 are viral persistence, either SARS-CoV-2 or RNAemia in tissues, persistent abnormalities in immune cells, changes in the inflammatory response, reactivation of latent pathogens, or autoimmune antibody development (Mantovani et al., 2022).

Regarding the neuropsychological long-term alterations described in the long-COVID syndrome (Frontera et al., 2021; Graham et al., 2021), memory is the predominant function altered, but also executive functions and visuospatial function (Ardila and Lahiri, 2020; Beaud et al., 2021; Jaywant et al., 2021; Llana et al., 2022). In this sense, when assessing memory, most studies were designed to detect declarative memory impairment, and other memory systems were not so profoundly explored (Llana et al., 2022). Declarative memory consists of memory for events and facts that are stored and can be explicitly retrieved (Squire et al., 2004). Several neuropsychological tests have been used to investigate the effects of the virus on declarative memory, such as the 16-item Grober and Buschke Free/Cued Recall Paradigm, the Corsi Block Tapping test, and the Rey Auditory Verbal Learning Test. These studies have found impairment in long-term verbal and visuospatial memory, as well as verbal learning (Llana et al., 2022). The neuroanatomical bases of declarative memory rely on the medial temporal lobe, including the hippocampus and other structures of the limbic system, which participates in memory and emotion (Catani et al., 2013).

SARS-CoV-2 causes olfactory dysfunction in many patients, being reported by long-COVID patients as a frequent symptom (Doty, 2022). Some possible causes of olfactory dysfunction are olfactory cleft obstruction, olfactory bulb atrophy, inflammation, downregulation of olfactory receptor proteins, and massive activation of macrophages and release of cytokines (Keshavarz et al., 2021; Xydakis et al., 2021; Frosolini et al., 2022). The virus can enter the olfactory bulbs and affect the brain through transcribriform or vascular routes (Brann et al., 2020). Studies have described how the virus can infect microglia and astrocytes, causing activation of these glial cells, and this effect may affect communication between neurons and neurogenesis (Vargas et al., 2020). In fact, neurogenesis is altered in the hippocampus of patients and rodents infected by the virus (Soung et al., 2022). Neuroimaging studies have detected that the hippocampus,

parahippocampal cortex, and amygdala, which are brain areas connected to the olfactory bulb, show degeneration and volume reduction in subjects suffering from mild COVID-19 infection (Douaud et al., 2022). Olfactory bulb dysfunction may extend to connected and proximal regions of the limbic systems that support memory (Kay, 2022). Studies that analyze the associations between symptoms and memory performance have found that olfactory dysfunction in long-COVID patients is frequently related to lower scores in tests assessing declarative memory (Damiano et al., 2022; Delgado-Alonso et al., 2022).

A different type of memory, which is supported by various brain systems, is procedural memory (Squire and Dede, 2015). This memory is not related to the limbic system function. The brain regions involved in procedural memory are the frontal and parietal cortices, the basal ganglia, and the cerebellum (Camina and Güell, 2017). Procedural memory is a type of implicit memory that aids the performance of specific tasks without conscious awareness of previous experiences, such as the stored motor programs of routine or well-rehearsed actions (Cubelli and Della-Sala, 2020). This memory has been poorly explored in long-COVID patients. Only studies assessing subjective complaints have reported forgetfulness related to how to do routine tasks in 15% of cases (Davis et al., 2021; Callan et al., 2022), and no studies to date have assessed this memory using objective measures of performance. Magnetic resonance imaging 2 weeks after hospital discharge in COVID survivors (Hafiz et al., 2022) or long-COVID patients (Besteher et al., 2022) showed basal ganglia and limbic system alterations in comparison with controls. These brain abnormalities were associated with fatigue symptoms in the post-acute phase (Hafiz et al., 2022).

Previous research points to medial temporal lobe dysfunction in long-COVID patients and suggests a relationship between medial temporal lobe dysfunction and olfactory dysfunction in these patients. Also, no published studies assessed procedural memory in long-COVID patients with objective tests. This type of memory is anatomically dissociated from the medial temporal lobe. This study assessed verbal declarative memory, procedural memory, general cognitive function, psychomotor speed, and incidental learning in long-COVID patients with and without anosmia and healthy individuals. The principal aims of the study were: (i) to determine the characteristics of procedural memory and declarative memory in long-COVID patients compared to healthy people; (ii) to investigate whether anosmia has adverse effects on the cognitive skills studied; and (iii) to explore possible differences in the relationship between the performance on the tests assessing procedural and declarative memories and the performance on the tests measuring general cognitive function, psychomotor speed, and incidental learning, mediated by the presence or absence of anosmia or long-COVID syndrome (**Figure 1**).

Materials and methods

Participants

Forty-two long-COVID participants (4 male) were recruited from several Spanish-long-COVID associations (Aragón, Asturias, Galicia, and Valencia). These participants met the criteria for inclusion following the World Health Organization's definition of long-COVID (World Health Organization [WHO], 2021): history of probable or confirmed SARS-CoV-2 infection with symptoms extending beyond 3 months from the onset of COVID-19, lasting for at least 2 months, and which cannot be explained by an alternative diagnosis. Participants were contacted via email and they were presented the study. Those who agreed to participate in the study completed online the Spanish adaptation of the National Health Service (NHS) Long COVID Pre- Assessment Questionnaire version 3 (National Health Service [NHS], 2021), that was used to explore clinical long-COVID symptomatology. Media was used for recruiting 30 additional healthy volunteers (12 male) that formed the control group (group C). Volunteers were invited through interviews on the radio, local newspapers and social media to contact via email with researchers of the study. Group C was included to obtain measures in a condition of health. All participants were Spanish native speakers without present or past severe neurological, psychological, or physical conditions or disorders that could potentially interfere with the results. Relevant sociodemographic information and clinical characteristics of the samples are shown and compared in **Table 1**.

This study was conducted in compliance with the European Community Council Directive 2001/20/EC and the Helsinki Declaration for biomedical research involving humans. The experimental data were collected after obtaining informed written consent from each subject. The study was approved by the local ethics committee.

Olfactory function assessment

The experience of olfactory function was assessed using an online Spanish adaptation of the NHS Long COVID Pre-Assessment Questionnaire version 3 (National Health Service [NHS], 2021). This was applied to long-COVID participants. In this questionnaire participants reported their original/acute COVID symptoms and long-COVID symptoms. They also answered to the Yes/No question "Do you have anosmia ("no sense of smell")?"

The sample of long-COVID patients was divided into two groups based on the presence or absence of anosmia in their reports. Patients of group A (n = 17) reported anosmia, while patients of group NA (n = 25) did not report anosmia.

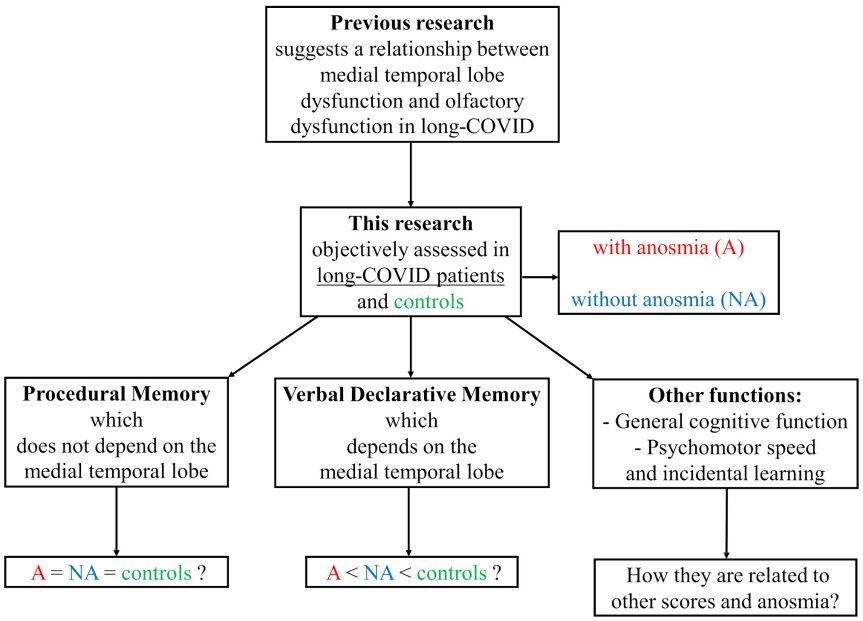

FIGURE 1
Research hypothesis diagram.

The sample was also divided into 4 groups according to the months elapsed from the COVID diagnosis to assessment (groups: ≤ 6-months, 7–12-months, 13–18-months, and ≥ 19-months; **Table 1**).

Procedural memory assessment

Procedural memory was assessed with the Mirror Tracing Test (MTT; Milner, 1962) (Model 58024E, Lafayette Instrument, USA), which measures the capacity to adapt to a novel trajectory within a sequence of practiced movements (Laforce and Doyon, 2002). MTT is an apparatus that contains a metal platform attached to a metal plate and a vertically hinged mirror. On the metal platform, there is the outline of a six-pointed star-shaped figure. The apparatus has a metal pen connected to the platform and to an automatic error-counter.

In each session, participants were seated in front of the MTT and prevented from seeing the six-pointed star-shaped figure directly by adjusting the metal plate. Thus, the star could only be seen through the vertical mirror. An investigator instructed the participants to trace the star with their dominant hand as quickly and accurately as possible while avoiding errors and remaining quiet. On each assessment day, participants were required to carry out four trials. Trials 1–4 (T1–T4) were completed on the first assessment day (Day 1), and trials T5–T8 on the following day (Day 2). Each trial had to be completed in a maximum of 10 min with a 10-s inter-trial interval in each session. The error rate (ER) was the total number of times the participant traced inside or outside the boundary lines of the star and was automatically recorded in each trial. Time per trial (TPT) was registered by the investigator with a standard stopwatch. Both parameters were assessed for all participants during the eight trials.

To measure procedural learning, the first two trials of Day 1 (T1–T2) were contrasted with the last two trials of Day 1 (T3–T4). To measure the consolidation of procedural learning, the first two trials of Day 2 (T5–T6) were contrasted with the last two trials of Day 1 (T3–T4). We also obtained subject-specific performance indices (expressed as percentages) of ER (ERI) and TPT (TPTI) for procedural learning (Day 1: ERI-d1 and TPTI-d1) and consolidation of learning (Day 2: ERI-d2 and TPTI-d2), using the following formulas:

ERI-d1 and TPTI-d1:

$$\frac{(T3+T4)-(T1+T2)}{(T1+T2)}$$

ERI-d2 and TPTI-d2:

$$\frac{(T5+T6)-(T3+T4)}{(T3+T4)}$$

The indices were negative when participants improved their performance over a given period. If the indices were near zero or positive, it was considered that there was no improvement.

Declarative memory assessment

Declarative memory was measured with the Spanish version of the Paired-Associate Learning (PAL) test

TABLE 1 Demographic information and clinical characteristics of the sample related to the COVID history.

	Sample (N = 72)	Group A (n = 17)	Group NA (n = 25)	Group C (n = 30)	P
Sex (F, M; M%)	56, 16; 22.2%	15, 2; 11.8%	23, 2; 8.0%	18, 12; 40.0%	0.009[b]
Age (Years)[a]	43 (35–49)	42 (31–46)	47 (41–51)	40 (34–50)	0.097[c]
SES[a]	6 (6–8)	7 (5–8)	6 (5–7)	6 (6–7)	0.136[c]
Annual income[a]	30 (20–40)	30 (20–30)	30 (20–40)	30 (20–40)	0.767[c]
Handedness (n, %)					0.506[b]
Right-hand	67, 93.1%	17, 100%	22, 88%	28, 93.3%	
Left-hand	4, 5.6%		2, 8%	2, 6.7%	
Ambidextrous	1, 1.4%		1, 4%		
Ethnicity (n, %)					0.316[b]
White	69, 95.8%	17, 100%	24, 96%	28, 93.3%	
Bla., Lat., Car., Afr.	2, 2.8%			2, 6.7%	
Prefer not to say	1, 1.4%		1, 4%		
BMI[a]	24 (22–29)	28 (22–31)	23 (21–27)	23 (21–27)	0.371[c]
ED Diagn. (n, %)	9, 12.5%	0, 0%	7, 28.0%	2, 6.7%	0.012[b]
Acute phase of COVID					
Hospit. (n, %)	9, 21.4%	3, 17.6%	6, 24%	N/A	0.622[b]
Vent. assist. (n, %)					0.486[b]
No	35, 83.3%	15, 88.2%	20, 80%	N/A	
Intubated	2, 4.8%		2, 8%	N/A	
Enhanced RS	5, 11.9%	2, 11.8%	3, 12%	N/A	
Long-COVID symptoms					
Months[a]	16 (8–19)	18 (5–22)	15 (10–18)	N/A	0.389[d]
≤6 (n)	9	5	4		
7–12 (n)	4	0	4		
13–18 (n)	18	7	11		
≥19 (n)	11	5	6		
Sense of taste					<0.001[b]
Ageusia (n, %)	9, 21.4%	8, 47.1%	1, 4%	N/A	
Metal. taste (n, %)	6, 14.3%	4, 23.5%	2, 8%	N/A	
Sleep disturb. (n, %)	33, 78.6%	14, 82.4%	19, 76%	N/A	0.622[b]
Nightmares (n, %)	21, 50%	5, 29.4%	16, 64%	N/A	0.028[b]
Cog. disturb (n, %)	42, 100%	17, 100%	25, 100%	N/A	N/A
Brain fog (n, %)	39, 92.9%	16, 94.1%	23, 92%	N/A	0.794[b]
Fatigue (n, %)	39, 92.9%	17, 100%	22, 88%	N/A	0.138[b]
Headache (n, %)	27, 64.3%	13, 76.5%	14, 56%	N/A	0.174[b]
Vis. disturb. (n, %)	32, 76.2%	13, 76.5%	19, 76%	N/A	0.972[b]
Rec. fevers (n, %)	9, 21.4%	5, 29.4%	4, 16%	N/A	0.298[b]
Myalgia (n, %)	36, 85.7%	14, 82.4%	22, 88%	N/A	0.608[b]
Joint pain (n, %)	37, 88.1%	14, 82.4%	23, 92%	N/A	0.343[b]
Chest pain (n, %)	24, 57.1%	9, 52.9%	15, 60%	N/A	0.650[b]
Tinnitus (n, %)	23, 54.8%	10, 58.8%	13, 52%	N/A	0.663[b]

[a]Data are shown as median (first quartile–third quartile); [b]Pearson chi-squared test; [c]Kruskal–Wallis test; [d]Mann-Whitney U-test. All the participants had > 12 years of education. SES, subjective socio-economic status (scale range from 1 to 10 points). Annual income is reported on a 5-point scale (ranging from 10 to 50 thousand euros). Bla., Lat., Car., Afr., Black, Latino, Caribbean or African; BMI, body mass index; ED diagn., emotional disorder diagnosis; Hospit., hospitalization; N/A, not applicable; Vent. assist., ventilatory assistance; RS, respiratory support; Months, months from diagnosis to assessment; Metal., metallic; Disturb., disturbance; Cog., cognitive; Vis., visual; Rec., recurrent.

from the Wechsler Memory Scale (WMS-III) (Wechsler, 1997). The task consists of eight paired-associate words with no semantic relationship, which must be learned, recalled, and recognized.

On Day 1, the paired words were learned in four learning trials (T1–T4). In each trial, the researcher read a list of eight paired words. After this, the participant performed an immediate cued-recall trial where the researcher presented the

first word of each pair and requested the immediate recall of its paired word. The order of presentation of the paired words varied through the four learning trials. A score was obtained for each of the 4 immediate cued-recall trials (maximum score per trial: 8). The sum of the four scores was computed to obtain the total number of correctly recalled pairs (PAR-I, maximum score: 32). The learning index was also obtained (PALI). PALI is the number of paired words correctly recalled in the last immediate cued-recall trial (Trial 4) contrasted with the number of paired words correctly recalled in first immediate cued-recall trial (Trial 1) (range score: −8 to +8, a higher value indicates higher learning across the four trials). Then, after 25–35 min, delayed cued-recall (PAR-D) was requested (PAR-d1). In PAR-d1 (maximum score: 8), the researcher requested the cued-recall of the paired words, giving the first word of each pair as a cue. Next, a delayed recognition trial was conducted (PARe-d1). In PARe-d1 (maximum score: 24), the participant was requested to recognize the previously presented pairs of words in a list of 24 pair-associated words, composed of 12 previously presented pairs (four duplicated) and 12 distractors. On Day 2, 24 h later, cued-recall (PAR-d2) (maximum score: 8) and recognition (PARe-d2) (maximum score: 24) were requested in the same way as described for the PAR-d1 and PARe-d1 trials.

Assessment of other cognitive abilities

The Spanish Version 8.1 of the Montreal Cognitive Assessment scale (MoCA; Nasreddine et al., 2005) was used to obtain a score of the overall level of cognitive abilities (maximum score: 30; cognitive impairment: <26).

Psychomotor speed, sustained attention, and incidental learning were measured with the Digit Symbol Substitution Test (DSST). This is a subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997). The DSST is a paper-and-pencil cognitive test that presents a coding matrix containing the digits 1–9 paired with a symbol. On the same page, a series of digits with a blank space for sketching the symbol is presented. Participants are requested to do the task as fast as possible. There is a time limit of 120 s to match the symbols with their corresponding numbers. When participants do not complete the first four lines of the task on time, more time is given to complete the full four lines to ensure enough experience with digit-symbol pairing. The DSST score consists of the number of correctly matched symbols in 120 s (DSS-M, maximum score: 133). Immediately after completing the task, the researcher gives the participant a new sheet of paper with the digits 1–9 in two lines. Participants are required to complete the blank spaces by drawing from memory the symbols paired with each number, with no time limit. This cued-recall task provides a measure of incidental learning (DSS-IL, maximum score: 18). Subsequently, participants were asked to draw all the symbols they could remember in a free-recall test without digits. In this task, free-recall of the incidental learning was registered (DSS-R, maximum score: 9).

Procedure

All participants individually completed the online sociodemographic questionnaire, and the long-COVID patients also completed the Long-COVID Pre-Assessment Questionnaire. Then, participants were scheduled separately to carry out the neuropsychological assessment in two consecutive sessions separated by 24 h (Day 1 and Day 2). On Day 1, participants completed the neuropsychological assessment in the following sequence: MTT, MoCA, PAL, DSST, delayed PAL tests. On Day 2, the sequence was: PAL and MTT. The session lasted no more than 45 min on Day 1 and no more than 20 min on Day 2. There was a 10-min rest between the MTT and MoCA on Day 1. Both sessions were held between 09:00 and 13:00 or between 16:00 and 20:00. Due to technical problems, 1 participant of group A, 2 participants of group NA and 1 participant of group C could not be assessed with the MTT.

Statistical analysis

Most of the variables had a non-normal distribution after applying the Shapiro-Wilk test, so we used the Kruskal–Wallis test to compare the groups' scores of the neuropsychological tests, and post-hoc multiple comparisons with Bonferroni correction when significant group effects were found. Additional Kruskal–Wallis tests compared the scores of the neuropsychological tests among the groups of patients divided according to the months elapsed from the infection to assessment (≤6, 7–12, 13–18, and ≥19-months). To study the relationship between the MoCA and DSST scores and the scores of the procedural and declarative memory tests (i.e., MTT and PAL) mediated by Group, non-parametric partial correlations were calculated separately for each group, considering these variables. All the correlations were calculated controlling for the variables Sex and Age. When a significant correlation coefficient was found, we tested significant differences in the coefficients between pairs of groups using Fisher's Z-test (Hidalgo et al., 2014). All the analyses were performed with the IBM SPSS Statistics, Version 26 (IBM Corp.). The level of statistical significance was set at $P < 0.05$. We used Kirk (1996) and Cohen's (1988) guidelines for the interpretation of the effect size of the Kruskal–Wallis tests, (η^2 = 0.06 = 0.14 medium; $\eta^2 \geq 0.14$ = large), and the strength of the correlations, (r = 0.3–0.5 medium; $r > 0.5$ = large), respectively.

Results

Group differences in procedural memory

Table 2 shows the Kruskal–Wallis tests and the statistic H, with its degrees of freedom and significance. There were group differences in the performance indices of Day 2 (ERI-d2 and TPT-d2, $Ps \leq 0.042$, $\eta^2 = 0.07$ and $\eta^2 = 0.08$, respectively, Figure 2). As mentioned, the higher these indices are, the less improvement they reflect. The post-hoc multiple comparisons with Bonferroni correction showed that the ERI-d2 index was higher in the participants of group A than in those of group NA ($P = 0.043$) but was similar in the participants of group C compared both to group A and group NA ($Ps \geq 0.148$, Figure 2). The TPTI-d2 index was higher in the group A than in the group C ($P = 0.022$) but was similar in group NA compared both to group A and group C ($Ps \geq 0.184$, Figure 2).

Group differences in declarative memory

Table 2 shows the statistics of the group comparisons. The participants' scores differed among the groups in the cued-recall tests (PAR-I, PAR-d1, and PAR-d2, all $Ps \leq 0.005$, $\eta^2 \geq 0.13$). The post-hoc tests showed that the participants of group A had lower scores than the participants of group C ($P = 0.002$), and the participants of group NA had similar scores as those of groups C and A ($Ps \geq 0.222$) in PAR-I (Figure 3). Besides this, the PAR-d1 and PAR-d2 scores were also lower in group A than in group C ($P = 0.003$ and $P = 0.011$, respectively; Figure 3). In addition, the PAR-d1 and PAR-d2 scores were lower in group NA than in group C ($P = 0.045$ and $P = 0.037$, respectively; Figure 3).

Group differences in other cognitive abilities

Table 2 presents group differences in the scores of the MoCA and the DSST tests. The participants of group A had lower scores than the participants of group C in the MoCA ($P = 0.001$, $\eta^2 = 0.21$, Figure 4) and in the DSST tests (DSS-M, DSS-IL and DSS-R: $P < 0.001$, $\eta^2 = 0.27$, $P = 0.043$, $\eta^2 = 0.08$, and $P = 0.026$, $\eta^2 = 0.08$, respectively, Figure 4). Also, the participants of group NA had lower scores than the participants of group C in the MoCA ($P = 0.017$, Figure 4) and the DSS-M ($P = 0.015$, Figure 4). However, the score of the A and NA groups was similar in all the tests ($Ps \geq 0.083$), and the scores of the NA and C groups did not differ in the DSS-IL and DSS-R tests ($Ps \geq 0.086$; Figure 4).

Scores of neuropsychological tests and months elapsed from the infection to assessment

The scores of the MoCA and DSST were similar among the groups of patients divided according to the months elapsed from the COVID diagnosis to assessment (MoCA: $H(3) = 3.27$, $P = 0.35$; DSS-M: $H(3) = 0.37$, $P = 0.95$; DSS-IL: $H(3) = 0.03$, $P = 0.99$; and DSS-R: $H(3) = 2.51$, $P = 0.47$). The same result was obtained when the scores of MTT and PAL were compared (ERI-d1 and ERI-d2: $Hs(3) \leq 0.48$, $Ps = 0.92$; TPTI-d1 and TPTI-d2: $Hs(3) \leq 3.15$, $Ps \geq 0.37$; PALI: $H(3) = 7.19$, $P = 0.06$; PAR-I: $H(3) = 2.24$, $P = 0.52$; PAR-d1 and PAR-d2: $Hs(3) \leq 6.03$, $Ps \geq 0.11$; and PARe-d1 and PARe-d2: $Hs(3) \leq 2.51$, $Ps \geq 0.47$).

Relationship between procedural memory and other cognitive abilities

Table 3 shows the correlation coefficients and their significant tests computed for each group. The scores of the ERI-d1 were negatively associated with the scores of the DSS-IL in group A ($P = 0.040$), showing that the lower the participants' incidental learning in the DSST, the more the errors they made in the procedural memory index (i.e., a higher score in ERI reflects less improvement over trials). Fisher's Z-test showed no differences between group A and group NA ($Z = -1.32$, $P = 0.187$) or group C ($Z = -1.84$, $P = 0.066$) in the correlation coefficient.

Relationship between declarative memory and other cognitive abilities

Table 3 presents the r and P-values computed for each group. The PALI scores were positively associated with the MoCA and DSS-M scores ($P = 0.014$ and $P = 0.048$, respectively) in the participants of group A. Fisher's Z-test comparing the correlation coefficient between PALI and MoCA showed that the coefficient was higher in group A compared both to group NA ($Z = 3.13$, $P = 0.002$), and group C ($Z = 3.00$, $P = 0.003$). The coefficient between PALI and DSS-M was higher in group A than in group NA ($Z = 2.15$, $P = 0.032$) but was similar in groups A and C ($Z = 1.07$, $P = 0.284$).

Concerning the cued-recall tests, the PAR-I scores were positively related to the MoCA and the DSS-R scores ($P = 0.049$ and $P = 0.019$, respectively) in the participants of group NA. Fisher's Z-tests failed to find differences between the coefficients for any comparison tested (coefficient between PAR-I and MoCA: $Z \leq 0.73$, $P \geq 0.465$; coefficient between PAR-I and DSS-R: $Z \leq 1.86$, $P \geq 0.063$). Besides, the PAR-d1 score was positively associated with the MoCA score in groups A and NA (all $Ps \leq 0.049$) and with the score of both the DSS-M and DSS-R

TABLE 2 Mean ± standard deviation of the study variables and group comparisons.

	Group A (N = 17)	Group NA (N = 25)	Group C (N = 30)	Kruskal–Wallis test	
				H-value (df = 2)	P-value
MoCA	25.81 ± 2.42	26.39 ± 2.64	28.07 ± 1.58	14.46	**0.001**
DSST					
DSS-M	64.50 ± 16.08	69.96 ± 17.92	84.59 ± 10.64	16.91	**<0.001**
DSS-IL	10.19 ± 4.79	10.35 ± 4.34	13.41 ± 3.71	7.70	**0.021**
DSS-R	6.81 ± 1.47	7.60 ± 0.99	7.83 ± 1.04	7.44	**0.024**
MTT					
ERI-d1	−21.98 ± 47.19	−21.85 ± 39.10	9.70 ± 153.19	0.01	0.994
ERI-d2	−9.01 ± 55.78	−49.81 ± 44.19	−38.37 ± 58.68	6.35	**0.042**
TPTI-d1	−30.41 ± 16.59	−28.08 ± 22.01	−27.37 ± 26.84	0.06	0.972
TPTI-d2	1.39 ± 32.01	−16.59 ± 33.37	−23.01 ± 18.37	7.29	**0.026**
PAL					
PALI	4.44 ± 2.16	4.00 ± 1.93	3.76 ± 1.57	0.51	0.776
PAR-I	14.94 ± 4.61	18.26 ± 8.03	21.34 ± 6.90	11.87	**0.003**
PAR-d1	5.06 ± 1.88	5.48 ± 2.29	6.72 ± 1.90	12.08	**0.002**
PAR-d2	4.94 ± 1.91	5.09 ± 2.29	6.52 ± 1.96	10.53	**0.005**
PARe-d1	23.50 ± 0.82	23.35 ± 1.72	23.86 ± 0.35	3.54	0.170
PARe-d2	23.69 ± 0.60	23.04 ± 2.25	23.79 ± 0.49	2.45	0.293

Significant difference is in bold. Df, degrees of freedom; Group A, anosmia; Group NA, absence of anosmia; Group C, control; MoCA, Montreal Cognitive Assessment scale; DSST, digit symbol substitution test; DSS-M, matching task of the DSST; DSS-IL, incidental learning of the DSST; DSS-R, free recall test of the DSST; MTT, Mirror Tracing Test; ERI-d1 and ERI-d2, error rate index on Day 1 and Day 2, respectively; TPTI-d1 and TPTI-d2, time per trial index on Day 1 and Day 2, respectively; PAL, Paired-Associate Learning; PALI, learning index; PAR-I, immediate cued-recall; PAR-d1 and PAR-d2, delayed cued-recall on Day 1 and Day 2, respectively; PARe-d1 and PARe-d2 = recognition on Day 1 and Day 2, respectively.

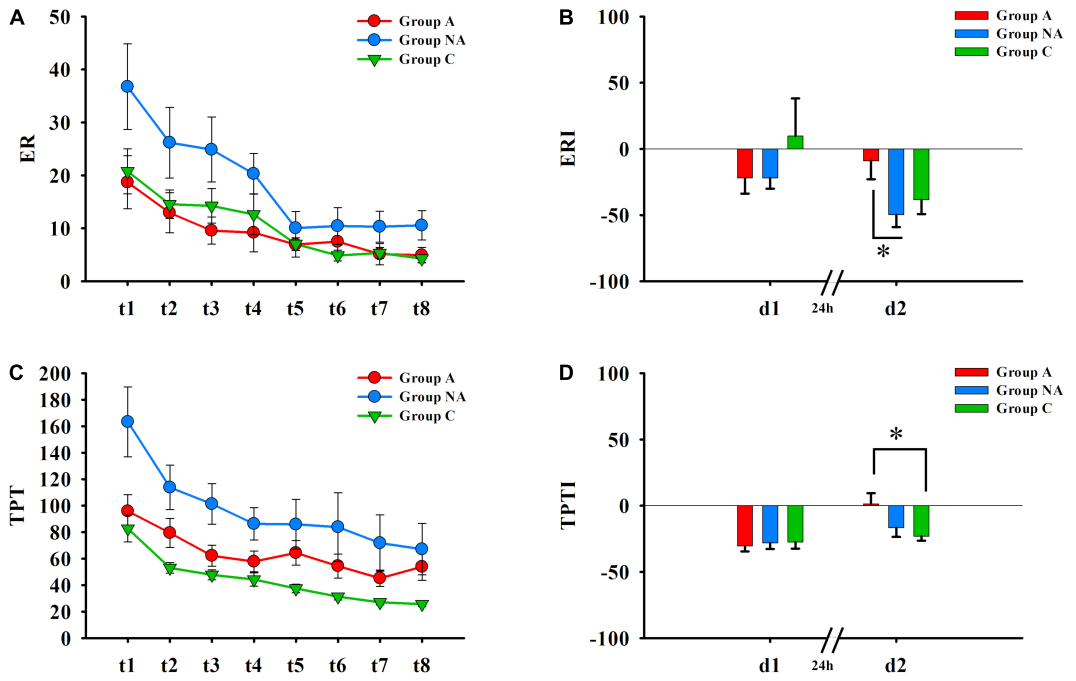

FIGURE 2
Procedural memory. **(A)** Error rates (ER) recorded during the eight trials (Day 1: t1–t4; Day 2: t5–t8) of the MTT. **(B)** Differences in ERI of day 1 (d1) and of day 2 (d2) among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *P = 0.043). **(C)** Time per trial (TPT) registered during the eight trials (Day 1: t1–t4; Day 2: t5–t8) of the MTT. **(D)** Differences in TPTI of day 1 (d1) and of day 2 (d2) among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *P = 0.022).

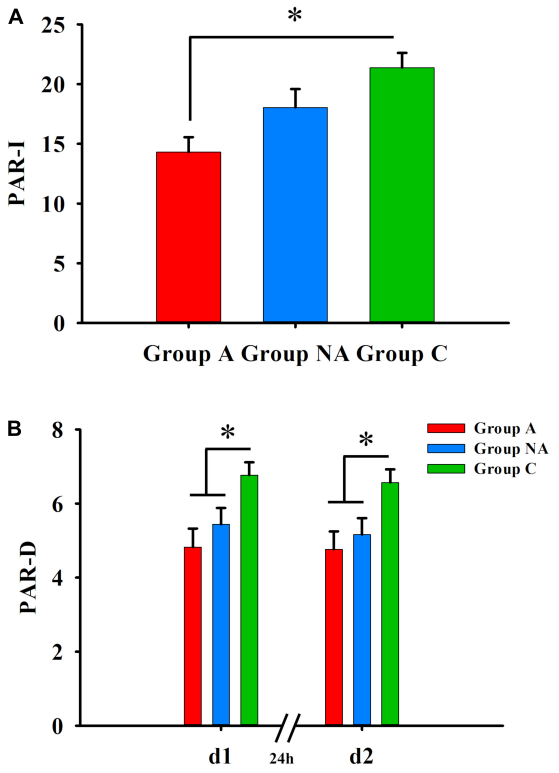

FIGURE 3
Declarative memory. **(A)** Differences in PAR-I among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *P = 0.002). **(B)** Differences in delayed cued-recall (PAR–D) PAR-d1 and PAR-d2 among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *$Ps \leq 0.045$).

in group NA (all $Ps \leq 0.044$). The correlation coefficient between PAR-d1 and MoCA was similar in all the groups (all $Zs \leq 1.16$, $Ps \geq 0.246$). Also, the coefficient between PAR-d1 and DSS-M was similar in all the groups (all $Zs \leq 1.09$, $Ps \geq 0.275$), and the same applied to the coefficient between PAR-d1 and DSS-R (all $Zs \leq 1.33$, $Ps \geq 0.183$). In addition, the PAR-d2 scores were positively related to the scores of the MoCA in groups A and NA (all $Ps \leq 0.026$) and to the DSS-M and DSS-R scores (all $Ps \leq 0.045$) in group NA. The groups showed similar correlation coefficients regarding the r-value between PAR-d2 and MoCA (all $Zs \leq 1.85$, $Ps \geq 0.064$) and between PAR-d2 and DSS-M (all $Zs \leq 1.46$, $Ps \geq 0.144$) and DSS-R (all $Zs \leq 0.88$, $Ps \geq 0.379$).

Regarding the tests of recognition, the PARe-d1 and PARe-d2 scores of the participants of group NA were positively associated with the MoCA (all $Ps \leq 0.030$) and DSS-M scores (all $Ps \leq 0.044$). The PARe-d1 score was also positively related to the DSS-IL score. Fisher's Z-test yielded no differences between group NA and groups A (Z = 1.96, P = 0.050) or C (Z = 1.61, P = 0.107) in the correlation coefficient between PARe-d1 and MoCA. The coefficient between PARe-d2 and MoCA was higher in group NA than in group C (Z = 2.33, P = 0.019) and was similar in groups NA and A (Z = 1.46, P = 0.144). The coefficient between PARe-d1 and DSS-M was higher in group NA than in group A (Z = 2.23, P = 0.025) and was equal in groups NA and C (Z = 1.48, P = 0.138). All the groups had similar r-values of the association between PARe-d2 and DSS-M (all $Zs \leq 1.84$, $Ps \geq 0.066$) and between PARe-d1 and DSS-IL (all $Zs \leq 1.71$, $Ps \geq 0.087$).

Discussion

This study objectively assessed long-COVID performance in dissociated memory systems, including olfactory dysfunction as a relevant symptom. It is the first work to evaluate consolidation of declarative and procedural learning in long-COVID. Results revealed that long-COVID participants, regardless of the presence or absence of anosmia, had lower cognitive ability than controls when assessed with the MoCA. Lower psychomotor speed and sustained attention than controls were also observed in all long-COVID participants when evaluated with DSST. However, the incidental learning score in DSST, both cue-guided and free-recalled, was exclusively altered in participants with anosmia compared to controls. In addition, both the MoCA and DSST scores were related to declarative memory function exclusively in the long-COVID groups, but not in healthy participants, who did not show altered memory processes and presented greater score homogeneity. When both acquisition and consolidation of explicit/declarative and implicit/procedural memory were assessed in long-COVID patients, we found that the long-term retention of both memories was more vulnerable than their acquisition. Acquisition was only negatively affected in participants with anosmia when compared to healthy subjects in the immediate recall of declarative memories. Also, long-COVID participants presented more impairment in cued-recall of declarative memory than in tests of recognition memory, which was preserved. The alteration of cued-recall declarative memory was independent of whether the test delay was short (i.e., 25–35 min) or long (i.e., 24 h). In addition, anosmia was linked to lower procedural memory when assessed during long delay. This symptom is also very relevant when we evaluated the immediate cued-recall of declarative memory, as only the participants with anosmia showed worse performance than the controls. However, all the patients with long-COVID syndrome, regardless of the presence or absence of anosmia, had worse performance than controls in the delayed versions of the cued-recall tests.

When assessing anosmia symptoms in the long-COVID sample, 40% of participants reported anosmia. Fernández-de-Las-Peñas et al. (2021) reviewed the prevalence of symptoms at onset and post-COVID when they were reported by both hospitalized and non-hospitalized adult patients. Data synthesis of the reviewed studies revealed that the pooled prevalence of anosmia is 45.7% (Fernández-de-Las-Peñas et al., 2021).

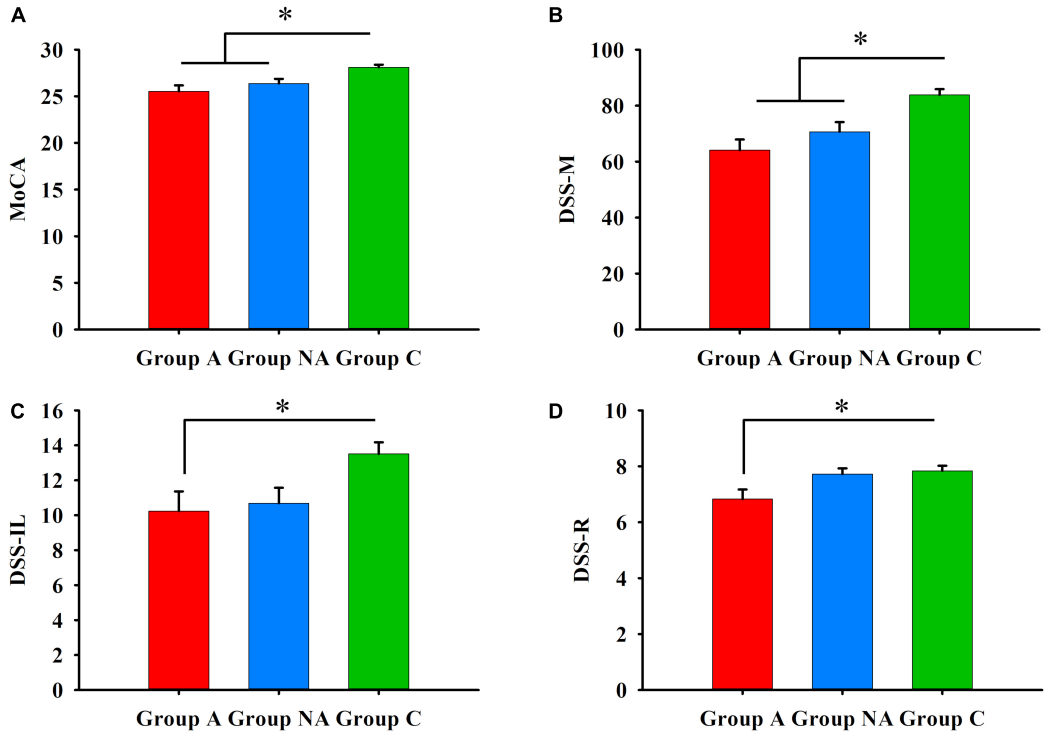

FIGURE 4
(A) General cognition. Differences in MoCA among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *$Ps \leq 0.017$).
(B) Psychomotor speed. Differences in DSS-M among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *$Ps \leq 0.015$).
(C) Incidental learning. Differences in DSS-IL among group A, group NA, and group C (Kruskal–Wallis test, Bonferroni correction. *$P = 0.043$).
(D) Incidental learning. Differences in DSS-R among A, NA, and C groups (Kruskal–Wallis test, Bonferroni correction. *$P = 0.026$).

The same pooled prevalence was reported in the review of Narayanan et al. (2022), showing that Europe, America, and Middle East present higher prevalence of olfactory dysfunction than Asia and Africa. Some of the studies performed in Europe that have used questionnaires and interviews including questions about the presence or absence of olfactory dysfunction in COVID-19 reported an anosmia prevalence of 33.9% (Giacomelli et al., 2020), 47% (Klopfenstein et al., 2020), 49% (Singer-Cornelius et al., 2021) 64% (Spinato et al., 2020), 65% (Menni et al., 2020), and 86% (Lechien et al., 2020b). When studies used olfactory psychophysical tests, they reported anosmia prevalence of 39% (Singer-Cornelius et al., 2021), 48% (Lechien et al., 2020a), and 67% (Vaira et al., 2020). Studies indicate that there is discrepancy between the results obtained with objective tests and subjective reports (Lechien et al., 2020a; Singer-Cornelius et al., 2021). There is a tendency to overestimate olfactory dysfunction when it is subjectively reported (Lechien et al., 2020a; Singer-Cornelius et al., 2021). The prevalence of subjectively reported anosmia in the present study was lower than that found in most of the studies described above, even considering studies that evaluate this symptom objectively.

Our results show that long-COVID participants, all adults aged under 51 years, presented lower scores than controls in general cognition. However, although situated at the suggested cut-off of 26 points (Nasreddine et al., 2005), their scores could not be considered indicative of abnormal cognitive performance. The memory impairment we observed when we evaluated declarative memory retrieval could be reflected in this global index. In fact, the general index of cognition obtained from the MoCA includes an assessment of short-term memory and working memory, and both are types of declarative memories. Therefore, associations between MoCA scores and PAL performance in long-COVID participants are not surprising.

Long-COVID participants presented worse psychomotor speed and sustained attention than controls, as shown when they performed the first part of the DSST test. These functions were assessed by DSST, which is sensitive to the presence of cognitive dysfunction in a wide range of clinical populations (Jaeger, 2018). However, this test may lack specificity in terms of the cognitive functions tested. Performance on DSST requires several cognitive functions, including planning, working memory, motor speed, attention, and visuoperceptual functions (Jaeger, 2018). In addition, associative learning, required for paired learning, could also affect performance on the first part of the DSST test by increasing speed. Associative learning may also contribute to incidental learning

TABLE 3 Non-parametric partial correlations controlling for sex and age.

		Group A (df = 12)				Group NA (df = 19)				Group C (df = 25)			
		MoCA	DSS-M	DSS-IL	DSS-R	MoCA	DSS-M	DSS-IL	DSS-R	MoCA	DSS-M	DSS-IL	DSS-R
ERI-d1	*r*	−0.111	−0.212	**-0.553**	−0.475	0.048	0.153	−0.151	0.035	0.001	−0.219	0.002	−0.194
	P	0.705	0.468	0.040	0.086	0.837	0.509	0.514	0.881	0.996	0.273	0.992	0.333
ERI-d2	*r*	−0.159	−0.062	0.160	0.173	−0.036	−0.239	−0.083	0.015	0.210	0.057	0.020	−0.139
	P	0.587	0.833	0.586	0.554	0.877	0.296	0.721	0.948	0.293	0.777	0.921	0.490
TPTI-d1	*r*	−0.385	−0.112	−0.491	−0.444	−0.033	−0.008	−0.136	−0.159	−0.121	0.062	−0.057	−0.248
	P	0.174	0.703	0.075	0.112	0.889	0.973	0.558	0.492	0.548	0.758	0.779	0.212
TPTI-d2	*r*	0.056	−0.375	0.079	−0.062	−0.113	−0.196	0.027	0.025	0.083	0.185	0.063	0.036
	P	0.849	0.187	0.788	0.833	0.627	0.394	0.907	0.914	0.679	0.357	0.755	0.858
PALI	*r*	**0.640**[a,b]	**0.536**[b]	0.360	0.291	−0.354	−0.135	0.131	0.127	−0.281	0.240	0.038	0.308
	P	0.014	0.048	0.206	0.313	0.115	0.558	0.571	0.583	0.156	0.227	0.850	0.118
PAR-I	*r*	0.211	−0.020	0.279	0.414	**0.434**	0.282	0.133	**0.508**	0.280	0.152	0.325	0.025
	P	0.470	0.946	0.335	0.141	0.049	0.215	0.567	0.019	0.157	0.449	0.098	0.901
PAR-d1	*r*	**0.551**	0.217	0.232	0.331	**0.435**	**0.443**	0.289	**0.528**	0.232	0.161	0.331	0.202
	P	0.041	0.456	0.424	0.247	0.049	0.044	0.205	0.014	0.243	0.422	0.091	0.312
PAR-d2	*r*	**0.592**	0.162	0.409	**0.615**	**0.589**	**0.599**	0.253	**0.441**	0.143	0.210	0.379	0.217
	P	0.026	0.580	0.147	0.019	0.005	0.004	0.268	0.045	0.477	0.293	0.052	0.276
PARe-d1	*r*	0.006	−0.187	0.005	0.080	**0.589**	**0.517**[b]	**0.529**	0.208	0.210	0.146	0.280	0.214
	P	0.985	0.521	0.986	0.786	0.005	0.016	0.014	0.367	0.292	0.468	0.157	0.285
PARe-d2	*r*	0.015	−0.151	−0.156	−0.308	**0.474**[c]	**0.444**	0.333	0.203	−0.152	0.078	0.094	0.040
	P	0.959	0.606	0.595	0.285	0.030	0.044	0.141	0.377	0.448	0.698	0.642	0.844

Significant difference is in bold. Correlation coefficient significantly different: [a]Group A vs. Group C; [b]Group A vs. Group NA; [c]Group NA vs. Group C. df, degrees of freedom; Group A, anosmia; Group NA, absence of anosmia; Group C, control; MoCA, Montreal Cognitive Assessment scale; DSS-M, DSS-IL, and DSS-R, matching task, incidental learning test and free recall test of the DSST, respectively; ERI-d1 and ERI-d2, error rate index of the MTT on Day 1 and Day 2, respectively; TPTI-d1 and TPTI-d2, time per trial index of the MTT on Day 1 and Day 2, respectively; PALI, learning index of the PAL; PAR-I, immediate cued-recall of the PAL; PAR-d1 and PAR-d2, delayed cued-recall of the PAL on Day 1 and Day 2, respectively; PARe-d1 and PARe-d2, recognition test of the PAL on Day 1 and Day 2, respectively.

when the individual remembers the pairs of symbols and numbers required in the second part of the task by both cued-guided recall and free recall (Jaeger, 2018). Therefore, it is not surprising that we found a relationship between performance on the PAL test, which requires learning and recall of pairs of words, and performance on DSST in long-COVID groups. The DSST has not been used previously to assess incidental learning after COVID-19 infection. The only study that has used this test evaluated exclusively digit-symbol pairing in recovered patients at a 1-month follow-up, finding impairment in this test (Gouraud et al., 2021). It is important to mention that the participants of this study differed from those of our study, as they did not meet the criteria for long-COVID diagnosis. However, psychomotor speed was altered in long-COVID patients with relevant neuropsychological symptoms or severe acute infection when assessing processing-speed deficits and sustained attention with the Symbol Digit Modalities Test (SDMT; Smith, 2007; Ferrucci et al., 2021; Ferrando et al., 2022) or other tests that provide an index of these functions (García-Sánchez et al., 2022; Vannorsdall et al., 2022; Zhao et al., 2022). From our DSST results, we can conclude that incidental learning, both cue-recalled (i.e., DSS-IL) or free-recalled (DSS-R), was exclusively altered in long-COVID participants who presented anosmia. Thus, the presence of anosmia, which is also a relevant factor accounting for difficulties in the immediate cued-recall of the PAL test, could reflect a greater vulnerability of brain regions involved in declarative learning. Declarative learning involves brain regions of the limbic system located in the medial temporal lobe (Clark et al., 2018). These structures, in turn, are closely related to olfactory dysfunction in COVID-hyposmia patients (Douaud et al., 2022; Morbelli et al., 2022).

This is the first study assessing implicit procedural learning in long-COVID. Previous literature has only mentioned the low prevalence of patients' self-reported difficulty to perform routine tasks (Davis et al., 2021; Callan et al., 2022). Results of procedural memory assessed with the MTT show that only the consolidation of procedural learning was affected in long-COVID participants presenting anosmia, with no differences between long-COVID and healthy subjects in the acquisition of this implicit memory. This highlights the importance of this symptom, which contributes exclusively to long-term procedural memory deficits, allowing us to propose the hypothesis about the specific association of olfactory dysfunction with the impairment of brain regions of the medial temporal lobe, such as the hippocampus. In fact, the role of the hippocampus in the consolidation of procedural memories, that

may initially require the involvement of the cerebellum or basal ganglia (Krakauer and Shadmehr, 2006), was revealed in a motor sequence task, similar to the MTT, which was performed one day after learning acquisition (Tucker et al., 2011; Schapiro et al., 2019). This means that basal ganglia and cerebellar cortex are involved in the initial storage of specific procedural memory tasks. However, this memory might be supported by other brain regions of the limbic system over time. Anosmia as a symptom in the long-COVID syndrome is frequently associated with the limbic system, both functionally (Damiano et al., 2022; Delgado-Alonso et al., 2022; Kay, 2022; Voruz et al., 2022; Yus et al., 2022) and structurally (Douaud et al., 2022; Morbelli et al., 2022). Therefore, a specific alteration of consolidation of procedural memory in long-COVID patients suffering from olfactory dysfunction is plausible. Studies assessing olfactory function in long-COVID have found that reported mental clouding was associated with more severe olfactory loss (Di Stadio et al., 2022). In addition, as in our study, olfactory loss was associated with cognitive impairment objectively assessed with neuropsychological tests of declarative memory (Damiano et al., 2022; Delgado-Alonso et al., 2022; Fiorentino et al., 2022).

When assessing verbal declarative memory, long-COVID participants presented more impairment in both delayed and long-term cued-recall tests than in recognition tests. This is consistent with previous research in long-COVID patients reporting impairment in verbal learning and verbal long-term memory when they were assessed with recall tests but not recognition tests of previously learned verbal material (Albu et al., 2021; García-Sánchez et al., 2022). However, other authors found that not only learning and recall but also verbal recognition, assessed with computerized tests, were impaired both in severe and mild long-COVID patients who presented temporal brain volume reduction (Widmann et al., 2021). Anosmia is relevant not only in the long-term recall but also in the immediate cued-recall of paired verbal items, suggesting that participants with this symptom are also vulnerable to an immediate evocation of verbal associations. The relationship between the difficulties in immediate verbal evocation and anosmia again shows that the presence of this symptom may indicate a higher predisposition to medial temporal lobe dysfunction, as the hippocampus is crucial both in the recognition and recall of declarative memories (Stark and Squire, 2000).

The findings of this study have implications for clinical practice. Long-COVID patients presented lower scores than controls in MoCA, but these scores were situated at the suggested cut-off of 26 points and considered indicative of normal cognitive performance. Therefore, a screening test, such as MoCA might fail to detect neuropsychological deficits in this population. In the light of the previously discussed results, the assessment protocol to detect cognitive deficits in this population should include declarative tests of long-term recall.

Strengths of this study are summarized in the following lines. The present study objectively assessed both procedural and declarative memory systems, as well as incidental learning, using neuropsychological tests in long-COVID patients who were assessed 3–28 months after COVID infection. This research is the first to compare procedural and declarative memories of long-COVID patients grouped on the basis of the presence or absence of olfactory dysfunction. The study not only examined learning, recall, and recognition memory processes, but it also evaluated long-term memory 24 h after acquisition. Finally, the study included a control group, consisting of participants without long-COVID, making possible to infer about the relative contribution of the infection to neurocognitive symptoms over and above the psychosocial effects related to the pandemic.

This study has some limitations. First, we do not know the pre-COVID neuropsychological function of the participants enrolled in this study. Thus, we cannot draw conclusions about a causal relationship between olfactory dysfunction and declarative and/or procedural memory impairment. Second, long-COVID participants in this study were evaluated 3–28 months after the acute phase of the COVID-19 infection by a subjective report of symptoms. Therefore, the characterization of anosmia was not provided by a standardized objective protocol. This report might be influenced not only by memory function but also by the individual's subjective perception. This limitation also applies to the reported symptoms at the time of assessment, which were not objectively assessed. Third, given the voluntary participation in the study, some subjects with a higher degree of long-COVID symptoms may have been less prone to accept enrollment in the study. Therefore, our findings cannot be generalized to the entire COVID-19 population.

In conclusion, the results of this research support that the consolidation of both procedural and declarative memories is more affected than the acquisition of these memories in long-COVID, which is also a clinical condition more vulnerable to deficits in delayed recall than in recognition of declarative memories. Assessment of explicit and implicit memories 24 h after acquisition reveals difficulties in memory consolidation in the long-COVID group compared to controls. This alteration in the consolidation of procedural memory is especially relevant in those long-COVID participants with associated anosmia, who also are more vulnerable to deficits in immediate recall of verbal declarative memory. This suggests that anosmia in COVID-19 could be associated with long-term limbic system dysfunction.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comité de Ética de la Investigación de la UPV (P04_16_02_2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

M-CJ, MM, and MM-L conceived and planned the experiments. M-CJ acquired the funding and administrated the project. CZ, MM, MM-L, and TL carried out the experiments. MM-L and TL contributed to the creation of the database. MM-L analyzed the data. CF and CZ designed the graphic representation. All authors drafted and reviewed the manuscript and approved its final version to be published and agreed to be accountable for all aspects of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between olfactory dysfunction and mood disturbances with objective and subjective cognitive deficits in long-COVID

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Background and purpose: The coronavirus disease 2019 (COVID-19) has been associated with olfactory dysfunction. The persistent symptoms of anosmia or hyposmia were associated in previous studies with the development of memory impairment and mood disturbances. We aimed to investigate the association between the chronicity of reported olfactory dysfunction and subjective and objective cognitive performance in long-COVID patients and to explore whether their emotional symptoms are related to their cognition.

Methods: One hundred twenty-eight long-COVID participants were recruited. Reported symptomatology, subjective memory complaints, anxiety and depression symptomatology, and trait-anxiety were assessed. Subjective memory complaints and mood disturbances were compared among groups of participants with olfactory dysfunction as an acute (AOD), persistent (POD), or nonexistent (NOD) symptom. Seventy-six of the volunteers also participated in a face-to-face session to assess their objective performance on tests of general cognitive function and verbal declarative memory. Objective cognitive performance and mood disturbances were compared among the AOD, POD, and NOD groups.

Results: The subjective memory complaints and the anxiety and depression symptoms were similar among the groups, but the score in general cognitive function was lower in the participants with symptoms of acute olfactory dysfunction than in those with no olfactory symptoms at any time. Participants' memory complaints were positively related to their emotional symptoms. The relationship between depressive symptomatology and memory complaints interacted with the olfactory dysfunction, as it only occurred in the participants without symptoms of olfactory dysfunction. Depressive symptomatology and acute olfactory symptoms were negatively associated with general cognitive function and delayed memory performance. The months elapsed from diagnosis to assessment also predicted delayed memory performance. Anxious symptomatology was negatively associated with the immediate ability to recall verbal information in participants who did not present olfactory dysfunction in the acute phase of the infection.

Conclusion: Olfactory dysfunction in the acute phase of the infection by COVID-19 is related to cognitive deficits in objective tests, and mood disturbances are associated

with self-reported and objective memory. These findings may contribute to further understanding the neuropsychological and emotional aspects of long-COVID.

KEYWORDS

long-covid, memory, cognition, anxiety, depression, olfactory dysfunction

1. Introduction

The novel coronavirus severe acute respiratory syndrome 2 (SARS-CoV-2), from which coronavirus disease 2019 (COVID-19) comes, has had an important impact at multiple levels (Hossain et al., 2020; Nicola et al., 2020). Following the World Health Organization (WHO), some of the most frequent symptoms in the acute phase of COVID-19 are fever, cough, tiredness, headache, and anosmia/dysgeusia (World Health Organization, 2021a), and these symptoms frequently disappear over time. However, around 10–20% of the people who had COVID-19 presented persistent symptoms (Greenhalgh et al., 2020; Carod-Artal, 2021). Long-COVID has been defined by WHO as a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis (World Health Organization, 2021b; Lai et al., 2022). Long-COVID is also known as long-haul COVID-19, post-COVID-19, post-acute COVID-19 and chronic COVID-19. Its aetiology is still unknown, although three principal theories are currently proposed: viral persistence, SARS-CoV-2 superantigen-mediated activation of the immune system, and autoimmunity (Brodin et al., 2022).

Olfactory dysfunction is a frequent symptom reported by long-COVID patients (Doty, 2022; Kay, 2022) and may have different causes (Doty, 2022). These include: (i) inflammation, infection and damage of the olfactory clef, the olfactory mucosa, and olfactory neuroepithelium, which could cause overreactive immune responses within the brain; (ii) downregulation of olfactory receptor proteins on the cilia of olfactory receptor cells; (iii) long-lasting damage of nervous system networks devoted to olfactory function, including the olfactory bulb, brain cells and capillary endothelial cells, in some cases, as a result of massive activation of macrophages and release of cytokines (Xydakis et al., 2021; Doty, 2022). High viral load in the nasal cavity and infected non-neuronal cells in the olfactory sensory epithelium can produce fast-onset anosmia caused by inflammation and with rapid remission (Doty, 2022). However, peripheral or central mechanisms may also be responsible for long-term olfactory disturbances. Cell damage or death of non-neuronal cells in the sensory epithelium, especially when basal cells are extensively damaged, downregulation of olfactory receptor genes (Zazhytska et al., 2022), and damage of olfactory sensory neurons could result in long-lasting olfactory disturbances (Doty, 2022). SARS-CoV-2 virus cannot invade olfactory sensory neurons using the transneuronal route (Brann et al., 2020) but it can enter the olfactory bulbs and affect the brain through transcribriform or vascular routes. In this way, it can infect many types of glial cells (Vargas et al., 2020), causing microglial and astrocytic activations that could affect synapses and neurons, as well as neurogenesis. The latter was altered in the hippocampus of patients and hamsters infected by the virus (Soung et al., 2022). Interestingly, chronic inflammation and suppressing hippocampal neurogenesis are associated with memory impairment and mood disorders, such as depression and anxiety (Chesnokova et al., 2016). Emotion and memory function might be affected by the suppression of hippocampal neurogenesis. The release of pro-inflammatory cytokines and the activation of microglia reduce adult hippocampal neurogenesis, which, in turn, causes mood and cognitive disturbances typically observed in chronic inflammatory disorders (Chesnokova et al., 2016). Damage to the olfactory bulb was demonstrated in long-COVID patients associated with long-term olfactory dysfunction (Frosolini et al., 2022). This damage might extend to proximal and connected regions, affecting the limbic system and, consequently, impairing emotional and memory networks (Díez-Cirarda et al., 2022; Goehringer et al., 2022; Kay, 2022; Martini et al., 2022). In fact, volume reduction and degeneration of brain areas connected to the olfactory bulb, such as the hippocampus, parahippocampal cortex, and the amygdala, with an important role in memory and emotional processing, were observed in brain scans of subjects who suffered mild COVID-19 infection (Douaud et al., 2022).

Long-term olfactory loss in long-COVID patients is associated with the development of neuropsychological alterations, including memory impairment (Kay, 2022) and mood disturbances. Previous studies which assessed memory in long-COVID patients have mainly explored declarative verbal memory (Llana et al., 2022b). These studies have found impairment in verbal learning, verbal short-term memory and verbal long-term memory assessed with neuropsychological tests such as the Rey Auditory Verbal Learning Test (RAVLT), in both hospitalised and non-hospitalised adults (Crivelli et al., 2022; García-Sánchez et al., 2022). Declarative verbal memory is essential to remember ongoing experiences and to learn new information about facts and events (Tulving and Markowitsch, 1998). Mood disturbances were related to memory impairment in previous research conducted in non-COVID population. In this sense, objective memory dysfunction assessed with neuropsychological tests was significantly associated with anxiety and depression (Arbabi et al., 2015). Also, self-reported memory complaints, assessed by different questionnaires in which participants report every-day subjective memory function, were also associated with anxiety and depression symptomatology in healthy subjects without objective memory impairment (Balash et al., 2013). Regarding declarative verbal memory, studies which objectively assessed this type of memory have found an association between declarative memory impairment and mood disorders (Biringer et al., 2007; Chepenik et al., 2012; Engelmann et al., 2020). In long-COVID population, many studies assessing the relevance of clinical symptoms have found an association between subjective memory complaints and depressive feelings (Titze de Almeida et al., 2022) or the presence of anxiety and depression (Almeria et al., 2020; Cysique et al., 2022). The study by Voruz et al. (2022) found that memory and mood disturbances in long-COVID patients who suffered a mild or moderate disease correlated with hyposmia and/or anosmia, suggesting that chronic olfactory dysfunction could be related to the impairment of the limbic system. In this way, declarative verbal memory, a memory system mainly supported by the

medial temporal lobe including the hippocampus and other limbic system structures (Catani et al., 2013), could be more impaired in long-COVID patients than other memory systems non-related to the limbic system function, such as procedural memory (Llana et al., 2022a). Olfactory dysfunction was associated not only with subjective memory complaints but also with objective verbal (Damiano et al., 2022) and episodic (Delgado-Alonso et al., 2022) memory performance, as well as with executive dysfunction and anxiety, but not depression (Delgado-Alonso et al., 2022). Specifically, the study of Cecchetti et al. (2022) found an association between dysgeusia and hyposmia during acute COVID-19 and increased vulneravility in declarative memory over time. However, more research is needed to better understand the interaction between chronic olfactory disturbances and memory and mood disturbances in long-COVID patients.

Based on the above issues, we hypothesised that there is an association between the chronicity of olfactory dysfunction and memory impairment, considering both self-rated and objective performance measures in long-COVID patients. Also, this memory impairment is predicted by negative emotional states. To address these hypotheses, we first considered as dependent variables the subjective memory complaints, anxiety and depression symptoms, and trait-anxiety in a sample of long-COVID patients divided into groups based on the presence of olfactory dysfunction as an acute (AOD), persistent (POD), or nonexistent (NOD) symptom. This division aims to distinguish initial anosmic/hyposmic patients from long-term anosmic/hyposmic patients. We compared the scores in these variables among the groups. Age, educational and socio-economic status and ventilatory assistance were also considered to control for their association with the dependent variables. Months from diagnosis to assessment, symptoms of anxiety and depression, and trait-anxiety were considered as independent variables predicting the memory complaints and considering the olfactory dysfunction as a factor that might interact with these predictions. Second, we further examined whether the objective memory performance in a hippocampal-dependent task, evaluated with a declarative verbal memory test, and cognitive function, assessed by a cognitive screening test, could differ among groups. We also determined the predictive value of the abovementioned independent variables in the objective memory performance and the contribution of the olfactory dysfunction to these predictions.

2. Materials and methods

2.1. Participants

This cross-sectional study was conducted in Spain between April 1 and September 23, 2022. Information about the study was disseminated *via* long-COVID associations and media.

This study was conducted in compliance with the European Community Council Directive 2001/20/EC and the Helsinki Declaration for biomedical research involving humans and approved by the ethics committee (UPV P04_16_02_2022). The experimental data were collected after obtaining written informed consent from each participant.

One hundred fifty-one individuals with long-COVID volunteered to participate. The study was finally completed by 132 of them. Four participants were excluded from the final sample because they did not meet the eligibility criteria. The final sample included 128 participants. Criteria for inclusion met with the standards of WHO definition of long-COVID (World Health Organization, 2021b) and were as follow: (1) History of probable or confirmed by RT-PCR or antigen tests SARS-CoV-2 infection at last tree months before the inclusion in the study. Probable SARS-CoV-2 infection refers to those symptomatic patients with suspected infection in their medical histories who did not undergo testing, as PCR testing or antigen tests were restricted to those who were more severely unwell early in the pandemic; (2) SARS-CoV-2 infection severity ranging from mild clinical symptoms without respiratory distress to severe respiratory distress with hospitalisation; (3) Symptoms temporally related to the SARS-CoV-2 infection which extend beyond 3 months from the onset of COVID-19 and last for at least 2 months and which cannot be explained by an alternative diagnosis. These symptoms can include at least two of the following manifestations: sensory changes (affecting olfactory, gustatory and/or visual function), fatigue, shortness of breath, fever, headache, myalgia, sleep disturbances, brain fog [concentration, memory, and executive function difficulties, which describes the feeling of being mentally slow, fuzzy, or spaced out, affecting the ability to think or concentrate (Asadi-Pooya et al., 2022)], or emotional disorders (mood and/or anxiety disorder); and (4) Native Spanish speakers or high proficieny in Spanish.

Exclusion criteria included: (1) Any cognitive complaint before COVID-19; (2) Past or present neurological disorder potentially associated with cognitive impairment and sensory impairment; (3) Present or previous severe psychological or psychiatric disorder; and (4) Uncontrolled medical conditions associated potentially biassing cognitive assessments.

2.2. Measurements and procedure

All participants completed the questionnaires described in section 2.2.1 online, and 76 of them comprised a non-probability subsample of individuals who voluntarily participated in an additional face-to-face session described in section 2.2.2.

2.2.1. On-line assessment

On-line assessment was performed using questionnaires that were sent out *via* email. Questions were presented in three Survey Monkey questionnaires for participants to complete at home without a set time or order. One questionnaire included items to collect sociodemographic data, as well as main symptoms using the Long COVID Pre Assessment Questionnaire (National Health Service, 2021). A further questionnaire assessed subjective memory with the Memory Failures in Every-day life (MFE; Sunderland et al., 1984). Finally, depressive and anxiety symptomatology were assessed using questions from the Goldberg Anxiety and Depression Scale (GADS; Goldberg et al., 1988) and trait-anxiety items of the brief version of the State–Trait Anxiety Inventory (STAI; Spielberger et al., 1970), which were condensed into a separate questionnaire. A more detailed description of these questionnaires is provided below.

Long-COVID symptomatology (including olfactory dysfunction) was collected using a Spanish adaptation of the National Health Service (NHS) Long COVID Pre Assessment Questionnaire version 3 (National Health Service, 2021). In this questionnaire, participants reported whether olfactory dysfunction was present both in the acute phase of the infection and at the time of assessment. This information was used to classify the participants into three groups: AOD group, which comprised individuals with olfactory dysfunction only in the acute phase of the disease (within 1 week post-infection); POD group, which included individuals presenting olfactory dysfunction from the initial

phase to the time of assessment (3–30 months post-infection); and NOD group, which gathered individuals without symptoms of olfactory dysfunction at any time.

Subjective memory complaints were assessed with MFE (Sunderland et al., 1984). We used the Spanish version of Montejo et al. (2012). The scale is composed of 28 items in which participants report the frequency of memory failures on a 3-point Likert scale ranging from 0 to 2 (maximum score: 56; Cronbach's alpha value in this study was 0.93). This questionnaire has three factors: memory of activities (MFEA; maximum score: 20), recognition (MFER; maximum score: 12), and communication monitoring (MFEC; maximum score: 24; Montejo et al., 2012).

Anxiety and depression symptomatology were assessed using the GADS (Goldberg et al., 1988). We employed a Spanish version of GADS (Monton et al., 1993) with 18 items (9 for anxiety and 9 for depression; the maximum score of each subscale is 9 with higher scores indicating more anxiety and/or depression). In this study, we obtained a Cronbach's alpha of 0.77. The stable tendency to attend to, experience, and report negative emotions (Gidron, 2013) was also measured by the trait-anxiety items of the brief version of the STAI (Spielberger et al., 1970), developed by Buela-Casal and Guillen-Riquelme (2017). This version of the scale presents 4 items of trait-anxiety (STAI-T). Items are rated on a 4-point Likert scale ranging from 0 to 3 (the maximum score is 12, with higher scores indicating more trait-anxiety). Cronbach's alpha value in this study was 0.74.

2.2.2. Face-to-face assessment

An individual session in the university facilities was conducted to assess the participants' current level of general cognitive function and objective declarative episodic memory performance ($n = 76$).

The Spanish Version 8.1 of the Montreal Cognitive Assessment scale (MoCA; Nasreddine et al., 2005) was used to obtain a score of the overall level of cognitive abilities (maximum score: 30; cognitive impairment: < 26).

In addition, a Spanish adaptation of the Paired-Associate Learning (PAL) from the Wechsler Memory Scale (WMS-III; Wechsler, 1997) was used to assess episodic verbal memory. The PAL task presents 8 pairs of words with no semantic relation. Participants have four recall tests to learn the maximum number of pairs. In each of the tests, the researcher provides the first word of the pair to the participant, who must say the word that accompanied it. The four learning tests provide an immediate recall score (PALIR; maximum: 32). Delayed recall (PALDR) and delayed recognition (PALDRe) are also evaluated 20–30 min later (maximum scores: 8 and 24, respectively).

2.3. Statistical analyses

Kolmogorov–Smirnov and Levene tests were performed to examine the normal distribution and homogeneity of the variances of the main variables of the data set, respectively. Most of the variables followed a non-normal distribution, so the group comparisons and correlations between the variables were calculated using non-parametric tests.

Kruskal-Wallis tests were used to compare the scores of the MFE, GADS, STAI, MoCA, and PAL among the AOD, POD, and NOD groups. Post-hoc multiple comparisons with Bonferroni correction were performed when significant group effects were found.

Hierarchical multiple regression was carried out to explore whether the criterion variable (i.e., MFE, MoCA or PAL) was predicted by the independent variable (i.e., months from diagnosis to assessment, symptoms of anxiety, symptoms of depression or trait-anxiety). The factor Group (i.e., AOD, POD, or NOD) was separately considered an interaction term to determine whether the relationship between the predictor variables and the criterion variables was different as a function of the olfactory dysfunction as an acute or persistent symptom. The AOD group, POD group, and NOD group were each operationalised as dichotomic variables for regression analyses. In each of the three variables, participants meeting the criteria for inclusion in the group were coded as 1, and participants who did not meet the criteria for inclusion in the group were coded as 0. The following control variables were included in the analyses as covariates: age, educational and socio-economic status, and ventilatory assistance. Using the ENTRY method, the covariates were entered as predictors in the first block. Then, the independent variable (i.e., months from diagnosis to assessment, symptoms of anxiety, symptoms of depression or trait-anxiety) and the Group (i.e., AOD, POD, or NOD) were entered as predictors in the second block; and the independent variable, the Group, and the variable computed by their interaction were entered as predictors in the third block.

Statistical analyses were performed using the IBM SPSS Statistics, Version 26 (IBM Corp.). The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

The characteristics of the final sample ($n = 128$) are described in Table 1, which includes, among other aspects, the subjective socio-economic status reported through the scale by Adler et al. (2000), annual income (consisting of one item that was rated on a 5-point scale ranging from 10 to 50 thousand euros), body mass index, hospital admission and level of respiratory support during the acute phase of COVID-19, and long-COVID symptoms (National Health Service, 2021). The characteristics of the subsample that underwent face-to-face assessment are described in Table 2, which includes the same aspects considered in Table 1. The percentage of participants with RT-PCR or antigen tests confirmed SARS-CoV-2 was 85.9% in the full sample and 90.8% in the subsample. The proportion of participants with RT-PCR or antigen tests confirmed SARS-CoV-2 was similar among groups (Tables 1, 2). The full sample and the subsample were comparable in demographic and clinical characteristics (all $Ps > 0.149$; see Supplementary File S1).

3.2. Differences based on the chronicity of the olfactory dysfunction

Table 3 presents the Kruskal-Wallis tests for the full sample of scores of the target variables and the statistic H, with its degrees of freedom and significance. Results showed that all the groups reported similar levels of memory complaints (MFE score and MFEA, MFER, and MFEC subscales, all $Ps \geq 0.20$). Similarly, the groups did not differ in their self-reported anxious and depressive symptomatology (all $Ps \geq 0.09$). The level of trait-anxiety was also similar in the groups (STAIT: $p < 0.16$).

Table 4 displays the descriptive statistics and the statistic H, with its degrees of freedom and significance, and the Kruskal-Wallis tests for the subsample in which we measured the general cognitive function (MoCA) and verbal episodic memory (PAL). In

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TABLE 1 Demographic information and clinical characteristics of the full sample related to the COVID history in the AOD, POD, and NOD groups.

	Full sample (N=128)	AOD group (*n*=22)	POD group (*n*=32)	NOD group (*n*=74)	*P*
Sex (F, M; M%)	114, 14; 10.9%	20, 2; 9.1%	30, 2; 6.3%	64, 10; 13.5%	.521[b]
Age (Years)[a]	45.50 (40–51)	44 (39.5–52.75)	44 (40–47.75)	47 (40.5–52)	.202[c]
SES[a]	7 (6–8)	8 (7–8.25)	7 (6–8)	6 (5–8)	.007[c]
Annual income[a]	30 (20–40)	35 (27.5–50)	25 (20–37.5)	30 (20–40)	0.045 [c]
Handedness (*n*, %)					.223[b]
Right-hand	118, 92.2%	20, 99.9%	32, 100%	66, 89.2%	
Left-hand	6, 4.7%	2, 9.1%		4, 5.4%	
Ambidextrous	4, 3.1%			4, 5.4%	
Ethnicity (*n*, %)					0.837 [b]
White	123, 96.1%	21, 95.5%	32, 100%	70, 94.6%	
Mixed ethnic groups	1, 0.8%			1, 1.4%	
Bla., Lat., Car., Afr.	3, 2.3%	1, 4.5%		2, 2.7%	
Prefer not to say	1, 0.8%			1, 1.4%	
Months[d]	17 (11–21; 3–30)	18 (12,5–25; 4–30)	18 (10.75–21; 3–29)	16 (11–21; 3–30)	0.536 [c]
BMI[a]	24.85 (21.82–29.39)	26.97 (21,98–29.27)	25,12 (21.67–30,72)	23.71 (21.86–29.53)	0.685 [c]
Acute phase of COVID					
Confirm. Test	110, 85,9%	21, 95,5%	30, 93,8%	59, 79,7%	.060[b]
Hospit. (*n*, %)	34, 26.6%	4, 18.2%	7, 21.9%	23, 31.1%	.382[b]
Vent. assist. (*n*, %)					.198[b]
Not applicable	104, 81.3%	17, 77.3%	28, 87.5%	59, 79.7%	
Intubated	6, 4.7%			6, 8.1%	
Enhanced RS	18, 14.1%	5, 22.7%	4, 12.5%	9, 12,2%	
Long-COVID symptoms					
Sense of taste					<.001[b]
Ageusia (*n*, %)	23, 18%	2, 9.1%	18, 56.3%	3, 4.1%	
Metal. taste (*n*, %)	22, 17.2%	5, 22.7%	8, 25%	9, 12.2%	
Fatigue (*n*, %)	122, 95.3%	20, 90.9%	31, 96.9%	71, 95.9%	.550[b]
Brain fog (*n*, %)	120, 93.8%	21, 95.5%	29, 90.6%	70, 94.6%	.693[b]
Lack concent. (*n*, %)	127, 99.2%	22, 100%	32, 100%	73, 98.6%	.692[b]
Sleep disturb. (*n*, %)	104, 81.3%	19, 86.4%	28, 87.5%	57, 77%	.356[b]
Nightmares (*n*, %)	61, 47.7%	12, 54.5%	14, 43.8%	35, 47.3%	.734[b]
Rec. fevers (*n*, %)	35, 27.3%	8, 36.4%	8, 25%	19, 25.7%	.579[b]
Headache (*n*, %)	89, 69.5%	18, 81.8%	25, 78.1%	46, 62.2%	.101[b]
Vis. disturb. (*n*, %)	90, 70.3%	11, 50%	25, 78.1%	54, 73%	.063[b]
Myalgia (*n*, %)	108, 84.4%	20, 90.9%	26, 81.3%	62, 83.8%	.616[b]
ED Diagn. (*n*, %)	22, 17.2%	4, 18.2%	6, 18.8%	12, 16.2%	.942[b]

[a]Data are shown as median (first quartile – third quartile).
[b]Pearson chi-squared test.
[c]Kruskal-Wallis test.
[d]Data are shown as median (first quartile – third quartile; minimum – maximum).

All the participants had > 12 years of education. SES = subjective educational and socio-economic status (scale range from 1 to 10 points). Annual income is reported on a 5-point scale (range from 10 to 50 thousand euros). Bla., Lat., Car., Afr. = Black, Latino, Caribbean or African; Months = months from diagnosis to assessment; BMI = body mass index; Confirm. Test = SARS-CoV-2 confirmed with antigen or PCR test; Hospit. = Hospitalisation; Vent. assist. = ventilatory assistance; RS = respiratory support; Metal. = metallic; Concent. = concentration; Disturb. = disturbance; Vis. = visual; Rec. = recurrent; ED diagn. = emotional disorder diagnosis based on clinical judgement (mood and/or anxiety disorders according to DSM-5 classification).

the same line as the results for the full sample, the groups did not differ in their self-rated levels of memory complaints, anxious and depressive symptomatology, or trait-anxiety (all $Ps \geq 0.39$). The immediate and delayed ability to recall verbal episodic information was similar among the groups (PALIR and PALDR: $Ps \geq 0.27$), and delayed recognition revealed no significant differences (PALDRe:

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TABLE 2 Demographic information and clinical characteristics of the face-to-face assessed subsample related to the COVID history in the AOD, POD, and NOD groups.

	Subsample (N=76)	AOD group (*n*=13)	POD group (*n*=19)	NOD group (*n*=44)	*P*
Sex (F, M; M%)	68, 8; 10.5%	12, 1; 7.7%	18, 1; 5.3%	38, 6; 13.6%	.571[b]
Age (Years)[a]	46 (40–51)	41 (38–47)	43 (40.5–47)	47 (41–53)	.086[c]
SES[a]	6 (5–8)	8 (7–8)	6 (5.5–7.5)	6 (5–7)	.047[c]
Annual income[a]	30 (20–40)	30 (30–50)	30 (20–30)	30 (20–40)	.232[c]
Handedness (*n*, %)					.433[b]
Right-hand	69, 90.8%	12, 92.3%	19, 100%	38, 86.4%	
Left-hand	4, 5.3%	1, 7.7%		3, 6,8%	
Ambidextrous	3, 3.9%			3, 6.8%	
Ethnicity (*n*, %)					.521[b]
White	73, 96.1%	12, 92.3%	19, 100%	42, 95.5%	
Mixed ethnic groups					
Bla., Lat., Car., Afr.	3, 3.9%	1, 7.7%		2, 4.5%	
Prefer not to say					
Months[d]	17 (11–20; 3–30)	20 (18–25; 4–30)	17 (7.5–19; 3–29)	16 (11.5–19; 4–30)	.058[c]
BMI[a]	25.53 (21.89–31.08)	27.59 (22.84–30.04)	24.86 (20.18–30.28)	24.92 (22.14–31.18)	.520[c]
Acute phase of COVID					
Confirm. Test	69, 90,8%	12, 92,3%	18, 94,7%	39, 88,6%	.728[b]
Hospit. (*n*, %)	17, 22.4%	1, 7.7%	2, 10.5%	14, 31.8%	.067[b]
Vent. assist. (*n*, %)					.302[b]
Not applicable	64, 84.2%	11, 84.6%	18, 94.7%	35, 79.5%	
Intubated	5, 6.6%			5, 11.4%	
Enhanced RS	7, 9.2%	2, 15.4%	1, 5.3%	4, 9.1%	
Long-COVID symptoms					
Sense of taste					<.001[b]
Ageusia (*n*, %)	15, 63.2%	1, 7.7%	13, 68.4%	1, 2.3%	
Metal. taste (*n*, %)	13, 17.1%	4, 30.8%	4, 21.1%	5, 11.4%	
Fatigue (*n*, %)	72, 94.7%	13, 100%	18, 94.7%	41, 93.2%	.626[b]
Brain fog (*n*, %)	70, 92.1%	12, 92.3%	17, 89.5%	41, 93.2%	.882[b]
Lack concent. (*n*, %)	75, 98.7%	13, 100%	19, 100%	43, 97.7%	.692[b]
Sleep disturb. (*n*, %)	62, 81.6%	11, 84.6%	16, 84.2%	35, 79.5%	.866[b]
Nightmares (*n*, %)	37, 48.7%	8, 61.5%	7, 36.8%	22, 50%	.376[b]
Rec. fevers (*n*, %)	18, 23.7%	6, 46.2%	4, 21.1%	8, 18.2%	.109[b]
Headache (*n*, %)	49, 64.5%	9, 69.2%	14, 73.7%	26, 59.1%	.499[b]
Vis. disturb. (*n*, %)	53, 69.7%	6, 46.2%	15, 78.9%	32, 72.7%	.112[b]
Myalgia (*n*, %)	65, 85.5%	13, 100%	14, 73.7%	38, 86.4%	.112[b]
ED Diagn. (*n*, %)	11, 14.5%	2, 15.4%	1, 5.3%	8, 18.2%	.407[b]

[a]Data are shown as median (first quartile – third quartile).
[b]Pearson chi-squared test.
[c]Kruskal-Wallis test.
[d]Data are shown as median (first quartile – third quartile; minimum – maximum).

All the participants had > 12 years of education. SES = subjective educational and socio-economic status (scale range from 1 to 10 points). Annual income is reported on a 5-point scale (range from 10 to 50 thousand euros). Bla., Lat., Car., Afr. = Black, Latino, Caribbean or African; Months = months from diagnosis to assessment; BMI = body mass index; Confirm. Test = SARS-CoV-2 confirmed with antigen or PCR test; Hospit. = Hospitalisation; Vent. assist. = ventilatory assistance; RS = respiratory support; Metal. = metallic; Concent. = concentration; Disturb. = disturbance; Vis. = visual; Rec. = recurrent; ED diagn. = emotional disorder diagnosis based on clinical judgement (mood and/or anxiety disorders according to DSM-5 classification).

$p = 0.40$). However, general cognitive ability was significantly different among the groups (MoCA: $p = 0.02$). The post-hoc multiple comparisons with Bonferroni correction showed that the general score of cognitive ability was lower in the participants with symptoms of acute olfactory dysfunction than in those with no olfactory symptoms at any time ($p = 0.02$, $\eta^2 = 0.08$; Figure 1). The

TABLE 3 Mean±standard deviation of the study variables and group comparisons in the full sample.

	AOD group	POD group	NOD group	Kruskal-Wallis test	
	(N=22)	(N=32)	(N=74)	*H*-value (*df*=2)	*p*-value
MFE	32.86 ± 7.96	33.88 ± 9.24	31.53 ± 11.65	0.99	0.61
MFEA	13.77 ± 3.19	15.03 ± 3.78	13.20 ± 4.85	3.23	0.20
MFER	3.09 ± 1.92	3.25 ± 2.14	3.14 ± 2.61	0.35	0.84
MFEC	16.00 ± 3.96	15.59 ± 4.36	15.19 ± 5.24	0.37	0.83
GADSA	6.41 ± 2.15	7.47 ± 1.48	6.80 ± 2.14	2.97	0.23
GADSD	5.23 ± 1.82	6.25 ± 1.41	6.01 ± 1.79	4.83	0.09
STAIT	4.64 ± 3.11	5.84 ± 2.53	5.70 ± 2.71	3.67	0.16

AOD group = acute olfactory dysfunction; POD group = persistent olfactory dysfunction; NOD group = absence of olfactory dysfunction; MFE = Memory Failures in Every-day life; MFEA = Memory of activities factor of the MFE; MFER = Recognition factor of the MFE; MFEC = Communication monitoring factor of the MFE; GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

TABLE 4 Mean±standard deviation of the study variables and group comparisons in the face-to-face assessed subsample.

	AOD group	POD group	NOD group	Kruskal-Wallis test	
	(N=13)	(N=19)	(N=44)	*H*-value (*df*=2)	*P*-value
MoCA	23.92 ± 2.93	25.84 ± 2.24	26.16 ± 3.03	7.46	**0.02**
PALIR	15.00 ± 4.88	14,47 ± 5.58	15.91 ± 7.28	0.83	0.66
PALDR	4.54 ± 1.90	5.26 ± 2.23	5.57 ± 2.29	2.64	0.27
PALDRe	23.31 ± 1.03	23.79 ± 0.42	23.11 ± 2.79	1.83	0.40
MFE	32.31 ± 8.17	32.74 ± 8.57	30.52 ± 12.26	0.43	0.81
MFEA	13,62 ± 3.57	14.74 ± 3.77	12.89 ± 5.19	1.79	0.41
MFER	3.08 ± 1.89	2.95 ± 2.15	2.89 ± 2.51	0.43	0.81
MFEC	15.62 ± 3.97	15.05 ± 3.94	14.75 ± 5.48	0.27	0.87
GADSA	6.00 ± 2.41	7.37 ± 1.50	6.80 ± 2.30	1.86	0.39
GADSD	5.38 ± 1.98	6.11 ± 1.45	6.07 ± 1.83	1.63	0.44
STAIT	4.62 ± 3.50	5.63 ± 2.14	5.52 ± 2.98	1.74	0.42

Significant difference is in bold. AOD group = acute olfactory dysfunction; POD group = persistent olfactory dysfunction; NOD group = absence of olfactory dysfunction; MoCA = Montreal Cognitive Assessment scale; PALIR = immediate recall score of the Paired-Associate Learning scale; PALDR = delayed recall score of the Paired-Associate Learning scale; PALDRe = recognition score of the Paired-Associate Learning scale; MFE = Memory Failures in Every-day life; MFEA = Memory of activities factor of the MFE; MFER = Recognition factor of the MFE; MFEC = Communication monitoring factor of the MFE; GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

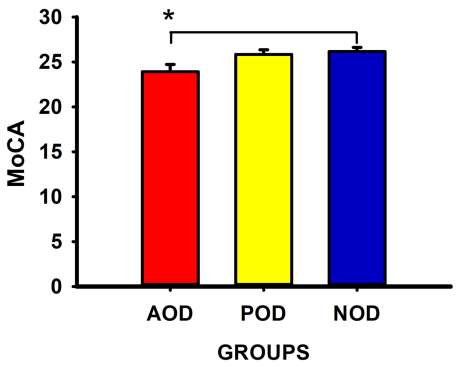

FIGURE 1
Montreal Cognitive Assessment (MoCA) scores (Mean±SEM) in the groups. AOD group=acute olfactory dysfunction; POD group=persistent olfactory dysfunction; NOD group=absence of olfactory dysfunction. *statistically significant, $p<0.05$.

MoCA score did not differ between the participants of the POD group and the participants of the AOD or NOD groups (all $Ps \geq 0.34$).

3.3. Months from diagnosis to assessment, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors of memory complaints

Table 5 shows the results of the multiple regression analyses, including standardised betas, their significance, and the model's general statistics. For simplification purposes, only the third block of each multiple regression is shown. The significant associations between scores of the MFE and main predictors are described below. The full scores of the MFE were predicted by anxious symptomatology and trait-anxiety in regression models that considered AOD (anxious symptomatology: $\beta = 0.329$, $p = 0.001$, 95% CI [0.733, 2.689]; trait-anxiety: $\beta = 0.400$, $p < 0.001$, 95% CI [0.803, 2.252]) and POD (anxious symptomatology: $\beta = 0.264$, $p = 0.006$, 95% CI [0.402, 2.341]; trait-anxiety: $\beta = 0.316$, $p = 0.001$, 95% CI [0.447, 1.939]) groups and after controlling for covariates. Thus, higher ratings on these variables were associated with higher subjective memory complaints. Also, considering depressive symptomatology as the main predictor, the full scores of the MFE were predicted by depressive symptomatology ($\beta = 0.342$, $p = 0.001$, 95% CI [0.919, 3.231]) by the AOD category ($\beta = 0.609$, $p = 0.027$, 95% CI [1.992, 31.765]) and the interaction term between depressive symptomatology and the AOD group ($\beta = -0.555$, $p = 0.040$, 95% CI [−5.391, −0.123]). Similarly, the MFE scores were predicted by the NOD category ($\beta = -0.821$, $p = 0.007$, 95% CI [−30.046, −4.736]) and the interaction term between depressive symptomatology and NOD group ($\beta = 0.797$, $p = 0.016$, 95% CI [0.479, 4.632]). Figures 2A,B depict these models graphically. Thus, depressive symptomatology was associated with memory complaints in participants who did not present olfactory

TABLE 5 Multiple regressions predicting self-rated memory failures (MFE score), with months since COVID-19 onset, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors.

Predictors	Criterion: MFE	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
Months,AOD	Age	−0.165	−1.763	0.080	−0.417, 0.024	0.081	0.035	1.024
	SES	−0.052	−0.564	0.574	−1.336, 0.743			
	Vent. Assist.	0.214	2.439	0.016	0.807, 7.768			
	Months	0.197	1.914	0.058	−0.010, 0.572			
	AOD	0.231	1.012	0.313	−6.118, 18.924			
	Months×AOD	−0.234	−1.012	0.313	−0.982, 0.318			
Months,POD	Age	−0.158	−1.658	0.100	−0.414, 0.037	0.087	0.041	0.898
	SES	−0.030	−0.341	0.733	−1.179, 0.832			
	Vent. Assist.	0.217	2.464	0.015	0.854, 7.842			
	Months	0.106	1.017	0.311	−0.143, 0.444			
	POD	−0.113	−0.498	0.620	−13.541, 8.102			
	Months×POD	0.217	0.948	0.345	−0.309, 0.876			
Months,NOD	Age	−0.147	−1.543	0.125	−0.400, 0.050	0.081	0.035	0.000
	SES	−0.055	−0.602	0.549	−1.367, 0.730			
	Vent. Assist.	0.222	2.501	0.014	0.924, 7.942			
	Months	0.143	0.997	0.321	−0.201, 0.610			
	NOD	−0.094	−0.412	0.681	−11.612, 7.609			
	Months×NOD	0.001	0.004	0.997	−0.514, 0.516			
GADSA, AOD	Age	−0.119	−1.409	0.161	−0.343, 0.058	0.140	0.098	1.073
	SES	−0.029	−0.331	0.741	−1.155, 0.824			
	Vent. Assist.	0.175	2.053	0.042	0.125, 6.883			
	GADSA	0.329	3.464	0.001	0.733, 2.689			
	AOD	0.337	1.210	0.229	−5.945, 24.624			
	GADSA×AOD	−0.286	−1.036	0.302	−3.392, 1.062			
GADSA, POD	Age	−0.114	−1.323	0.188	−0.341, 0.068	0.131	0.088	0.045
	SES	−0.019	−0.223	0.824	−1.081, 0.862			
	Vent. Assist.	0.183	2.110	0.037	0.226, 7.107			
	GADSA	0.264	2.802	0.006	0.402, 2.341			
	POD	−0.041	−0.100	0.920	−20.574, 18.594			
	GADSA×POD	0.089	0.212	0.832	−2.326, 2.885			
GADSA, NOD	Age	−0.110	−1.286	0.201	−0.334, 0.071	0.140	0.097	0.516
	SES	−0.034	−0.387	0.700	−1.186, 0.799			
	Vent. Assist.	0.181	2.093	0.038	0.196, 7.033			
	GADSA	0.190	1.324	0.188	−0.488, 2.460			
	NOD	−0.306	−0.971	0.334	−19.693, 6.733			
	GADSA×NOD	0.237	0.718	0.474	−1.168, 2.499			
GADSD, AOD	Age	−0.110	−1.300	0.196	−0.331, 0.069	0.145	0.103	4.295
	SES	−0.002	−0.026	0.979	−1.005, 0.978			
	Vent. Assist.	0.172	1.999	0.048	0.033, 6.839			
	GADSD	0.342	3.554	0.001	0.919, 3.231			
	AOD	0.609	2.245	0.027	1.992, 31.765			
	GADSD×AOD	−0.555	−2.073	0.040	−5.391, −0.123			
GADSD, POD	Age	−0.102	−1.178	0.241	−0.327, 0.083	0.119	0.076	0.805
	SES	0.001	0.013	0.990	−0.979, 0.991			
	Vent. Assist.	0.167	1.895	0.060	−0.149, 6.849			
	GADSD	0.271	2.798	0.006	0.481, 2.806			
	POD	0.388	1.045	0.298	−8.388, 27.143			
	GADSD×POD	−0.340	−0.897	0.371	−4.079, 1.535			

(Continued)

TABLE 5 (Continued)

Predictors	Criterion: MFE	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
GADSD, NOD	Age	−0.100	−1.189	0.237	−0.319, 0.080	0.163	0.121	5.937
	SES	−0.004	−0.047	0.963	−1.011, 0.964			
	Vent. Assist.	0.164	1.922	0.057	−0.099, 6.683			
	GADSD	−0.011	−0.085	0.932	−1.691, 1.552			
	NOD	−0.821	−2.721	0.007	−30.046, −4.736			
	GADSD×NOD	0.797	2.437	0.016	0.479, 4.632			
STAIT, AOD	Age	−0.142	−1.698	0.092	−0.367, 0.028	0.173	0.132	2.819
	SES	−0.036	−0.419	0.676	−1.177, 0.766			
	Vent. Assist.	0.165	1.959	0.052	−0.035, 6.659			
	STAIT	0.400	4.175	<0.001	0.803, 2.252			
	AOD	0.313	1.937	0.055	−0.190, 17.548			
	STAIT×AOD	−0.270	−1.679	0.096	−2.857, 0.235			
STAIT, POD	Age	−0.117	−1.367	0.174	−0.342, 0.063	0.152	0.110	0.041
	SES	−0.025	−0.295	0.769	−1.099, 0.814			
	Vent. Assist.	0.163	1.882	0.062	−0.169, 6.694			
	STAIT	0.316	3.270	0.001	0.447, 1.939			
	POD	0.106	0.510	0.611	−7.379, 12.506			
	STAIT×POD	−0.044	−0.203	0.839	−1.739. 1.415			
STAIT, NOD	Age	−0.120	−1.431	0.155	−0.341, 0.055	0.180	0.139	2.702
	SES	−0.050	−0.592	0.555	−1.257, 0.678			
	Vent. Assist.	0.162	1.919	0.057	−0.103, 6.589			
	STAIT	0.166	1.333	0.185	−0.309, 1.579			
	NOD	−0.396	−2.135	0.035	−16.185, −0.609			
	STAIT×NOD	0.348	1.644	0.103	−0.214, 2.308			

The following covariates were included in the analyses: Age, SES and Ventilatory assistance. Significant *p*-values are underlined. *β* shows standardised values. Dichotomisation of the symptoms of olfactory dysfunction is 0 (no) and 1 (yes) for the following: AOD (acute olfactory dysfunction), POD (persistent olfactory dysfunction), NOD (absence of olfactory dysfunction); Covariates: Age, SES [subjective educational and socio-economic status (scale range from 1 to 10 points)], and Vent. Assist. [Ventilatory assistance: not applicable (0), enhanced respiratory support (1) and intubated (2)]. Months = months from diagnosis to assessment. GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

dysfunction in the acute phase of the infection (Figure 2A), and this interaction was mainly explained by the contribution of the group's NOD category, which comprised participants not suffering from olfactory dysfunction (Figure 2B).

3.4. Months from diagnosis to assessment, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors of general cognitive function

Table 6 shows the results of the multiple regression analyses and their main statistics. Only the third block of each multiple regression is shown. The significant associations between scores of the MoCA and main predictors are described below. Considering depressive symptomatology as the main predictor, and controlling for covariates, the scores of the MoCA were predicted by depressive symptomatology ($\beta = -0.262$, $p = 0.042$, 95% CI [−0.849, −0.015]) and by the AOD category ($\beta = -0.69$, $p = 0.048$, 95% CI [−10.568, −0.044]). The more symptomatology, the lower the scores in this test.

3.5. Months from diagnosis to assessment, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors of the ability to recall verbal information

Tables 7, 8 present the results of the multiple regression analyses and their main statistics. Only the third block of each multiple regression is shown. Immediate recall and delayed recall are the criterion variables in Tables 7, 8, respectively. The significant associations are described below. Regarding anxious symptomatology (Table 7), the PALIR scores were predicted by the AOD category ($\beta = -0.713$, $p = 0.037$, 95% CI [−23.671, −0.730]) and the interaction term between anxious symptomatology and AOD group ($\beta = 0.674$, $p = 0.044$, 95% CI [0.051, 3.488]). Thus, anxious symptomatology was associated with the immediate ability to recall verbal information in participants who did not present olfactory dysfunction in the acute phase of the infection, the greater the number of anxious symptoms, the lower the PALIR score (Figure 2C). The months elapsed from diagnosis to assessment predicted the scores of the PALDR (Table 8) in regression models that considered AOD and NOD

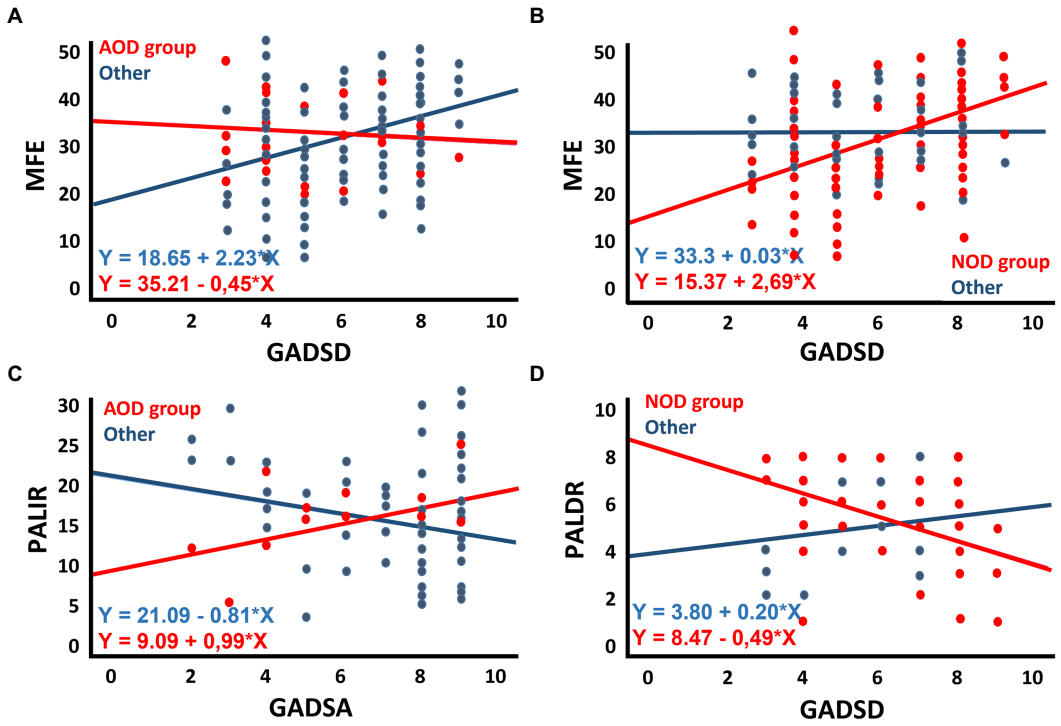

FIGURE 2
Scatter plots illustrating: **(A)** the interaction of depressive symptomatology (GADSD) in the groups of participants with or without acute olfactory dysfunction (with: AOD) in predicting memory complaints (MFE); **(B)** the interaction of depressive symptomatology (GADSD) in the groups of participants with or without symptoms of olfactory dysfunction (without: NOD) in predicting memory complaints (MFE); **(C)** the interaction of anxious symptomatology (GADSA) in the groups of participants with or without acute olfactory dysfunction (with: AOD) in predicting immediate ability to recall verbal episodic information (PALIR); **(D)** the interaction of depressive symptomatology (GADSD) in the groups of participants with or without olfactory dysfunction (without: NOD) in predicting delayed ability to recall verbal episodic information (PALDR).

groups and after controlling for covariates (AOD: $\beta = -0.325$, $p = 0.021$, 95% CI [−0.173, −0.014]; NOD: $\beta = -0.435$, $p = 0.013$, 95% CI [−0.223, −0.027]). Thus, the more months elapsed the lower the scores in this test. Also, the scores of the PALDR were predicted by depressive symptomatology ($\beta = -0.322$, $p = 0.015$, 95% CI [−0.687, −0.078]) and by the AOD category ($\beta = -0.818$, $p = 0.021$, 95% CI [−8.370, −0.689]). The more symptomatology, the lower the scores in PALDR. Also, the PALDR scores were predicted by the NOD category, which included participants without olfactory dysfunction ($\beta = 1.125$, $p = 0.005$, 95% CI [1.460, 8.043]) and the interaction term between depressive symptomatology and NOD group ($\beta = -1.048$, $p = 0.016$, 95% CI [−1.199, −0.126]). Depressive symptomatology was associated with the delayed recall score in participants who did not present olfactory dysfunction, the more symptomatology, the lower the scores (Figure 2D).

4. Discussion

The present study is the first to determine the relevance of olfactory dysfunction, categorised as an acute or a persistent symptom of long-COVID, in the explanation of subjective and objective memory scores, general cognitive function, and mood disturbances. Results revealed no differences among the NOD, AOD, and POD groups in subjective memory complaints, depression and anxiety-related symptoms or levels of trait-anxiety. The three groups presented similar self-rated memory failures in every-day life regarding activities with either a prospective or retrospective memory component, recognition of places and people, and communication monitoring. They were also comparable in terms of their anxiety and depression symptomatology and trait-anxiety. Concerning the association of these scores in our long-COVID participants, higher depression and anxiety-related symptoms and level of trait-anxiety were associated with reporting more subjective memory failures. These associations were found after controlling for participants' age, ventilatory assistance, and educational and socio-economic status. Our study revealed that the predictive value of the depressive symptoms for subjective memory failures is significantly stronger in individuals with no olfactory dysfunction. When assessing objective memory performance in a subsample of participants, those reporting olfactory dysfunction only during the acute phase of the disease presented lower scores in general cognition as assessed by MoCA than participants who had not experienced olfactory dysfunction. These lower scores were associated with depressive symptomatology after including covariates in the analyses. Self-reported memory failures were predicted by emotional symptoms in regression models that considered olfactory dysfunction. In addition, the association between depressive symptomatology and memory complaints was found specifically in the participants not suffering from olfactory dysfunction. Anxious symptomatology was negatively associated with the immediate ability to recall verbal information in participants who did not present olfactory dysfunction in the acute phase of the infection. The delayed recall of verbal information was predicted by depressive symptomatology in the regression model that considered the acute olfactory dysfunction. Besides, the more depressive symptomatology, the lower the delayed recall scores of the participants who did not present olfactory

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TABLE 6 Multiple regressions predicting general cognitive function (MoCA score), with months since COVID-19 onset, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors.

Predictors	Criterion: MoCA	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
Months,AOD	Age	−0.075	−0.584	0.561	−0.103, 0.057	0.143	0.068	0.157
	SES	−0.124	−1.058	0.294	−0.602, 0.185			
	Vent. Assist.	−0.141	−1.199	0.235	−1.964, 0.490			
	Months	−0.136	−0.985	0.328	−0.166, 0.056			
	AOD	−0.366	−1.069	0.289	−8.059, 2.437			
	Months×AOD	0.140	0.397	0.693	−0.203, 0.303			
Months,POD	Age	−0.027	−0.206	0.838	−0.090, 0.073	0.094	0.014	0.040
	SES	−0.171	−1.442	0.154	−0.689, 0.111			
	Vent. Assist.	−0.135	−1.109	0.271	−1.981, 0.566			
	Months	−0.184	−1.261	0.212	−0.191, 0.043			
	POD	0.029	0.109	0.914	−3.371, 3.759			
	Months×POD	−0.053	−0.201	0.842	−0.232, 0.190			
Months,NOD	Age	−0.081	−0.610	0.544	−0.108, 0.057	0.131	0.054	0.203
	SES	−0.135	−1.148	0.255	−0.623, 0.168			
	Vent. Assist.	−0.160	−1.342	0.184	−2.085, 0.409			
	Months	−0.206	−1.186	0.240	−0.223, 0.057			
	NOD	0.090	0.317	0.752	−2.805, 3.863			
	Months×NOD	0.131	0.450	0.654	−0.142, 0.225			
GADSA, AOD	Age	−0.113	−0.964	0.338	−0.108, 0.037	0.137	0.062	0.224
	SES	−0.119	−1.012	0.315	−0.595, 0.194			
	Vent. Assist.	−0.133	−1.132	0.262	−1.922, 0.530			
	GADSA	−0.113	−0.875	0.384	−0.497, 0.194			
	AOD	−0.428	−1.298	0.199	−8.362, 1.770			
	GADSA×AOD	0.152	0.473	0.638	−0.579, 0.939			
GADSA, POD	Age	−0.11	−0.892	0.376	−0.111, 0.042	0.072	−0.008	0.816
	SES	−0.181	−1.533	0.130	−0.703, 0.092			
	Vent. Assist.	−0.143	−1.157	0.251	−2.036, 0.541			
	GADSA	0.004	0.029	0.977	−0.338, 0.348			
	POD	0.485	0.884	0.380	−4.076, 10.565			
	GADSA×POD	−0.506	−0.903	0.370	−1.437, 0.541			
GADSA, NOD	Age	−0.144	−1.177	0.243	−0.121, 0.031	0.106	0.028	0.04
	SES	−0.142	−1.204	0.233	−0.639, 0.158			
	Vent. Assist.	−0.16	−1.329	0.188	−2.102, 0.422			
	GADSA	0.001	0.004	0.997	−0.514, 0.516			
	NOD	0.298	0.759	0.450	−2.848, 6.347			
	GADSA×NOD	−0.085	−0.201	0.842	−0.714, 0.583			
GADSD, AOD	Age	−0.116	−1.022	0.310	−0.107, 0.034	0.180	0.109	1.457
	SES	−0.108	−0.947	0.347	−0.568, 0.202			
	Vent. Assist.	−0.098	−0.837	0.405	−1.746, 0.714			
	GADSD	−0.262	−2.067	0.042	−0.849, −0.015			
	AOD	−0.690	−2.012	0.048	−10.568, −0.044			
	GADSD×AOD	0.409	1.207	0.232	−0.355, 1.444			

(Continued)

TABLE 6 (Continued)

Predictors	Criterion: MoCA	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
GADSD, POD	Age	−0.103	−0.842	0.403	−0.108, 0.044	0.084	0.005	0.297
	SES	−0.174	−1.484	0.142	−0.691, 0.101			
	Vent. Assist.	−0.108	−0.857	0.395	−1.893, 0.756			
	GADSD	−0.117	−0.882	0.381	−0.632, 0.244			
	POD	0.267	0.548	0.586	−4.715, 8.284			
	GADSD×POD	−0.271	−0.545	0.588	−1.337, 0.764			
GADSD, NOD	Age	−0.137	−1.15	0.254	−0.117, 0.031	0.138	0.063	0.864
	SES	−0.129	−1.105	0.273	−0.609, 0.175			
	Vent. Assist.	−0.117	−0.966	0.337	−1.885, 0.655			
	GADSD	−0.025	−0.136	0.892	−0.642, 0.560			
	NOD	0.585	1.462	0.148	−1.251, 8.123			
	GADSD×NOD	−0.405	−0.929	0.356	−1.120, 0.408			
STAIT, AOD	Age	−0.121	−1.041	0.302	−0.110, 0.035	0.141	0.066	1.020
	SES	−0.134	−1.143	0.257	−0.619, 0.168			
	Vent. Assist.	−0.146	−1.23	0.223	−2.009, 0.476			
	STAIT	−0.05	−0.379	0.706	−0.317, 0.216			
	AOD	−0.435	−2.135	0.036	−6.474, −0.219			
	STAIT×AOD	0.207	1.01	0.316	−0.263, 0.802			
STAIT, POD	Age	−0.109	−0.905	0.368	−0.109, 0.041	0.107	0.029	3.433
	SES	−0.184	−1.59	0.117	−0.702, 0.079			
	Vent. Assist.	−0.166	−1.356	0.179	−2.155, 0.411			
	STAIT	0.136	1.075	0.286	−0.118, 0.394			
	POD	0.514	1.677	0.098	−0.653, 7.535			
	STAIT×POD	−0.579	−1.853	0.068	−1.313, 0.048			
STAIT, NOD	Age	−0.151	−1.248	0.216	−0.122, 0.028	0.107	0.029	0.025
	SES	−0.149	−1.256	0.213	−0.650, 0.148			
	Vent. Assist.	−0.176	−1.439	0.155	−2.198, 0.356			
	STAIT	0.023	0.122	0.903	−0.352, 0.398			
	NOD	0.19	0.769	0.444	−1.775, 4.004			
	STAIT×NOD	0.045	0.157	0.876	−0.437, 0.512			

The following covariates were included in the analyses: Age, SES and Ventilatory assistance. Significant *p*-values are underlined. *β* shows standardised values. Dichotomisation of the symptoms of olfactory dysfunction is 0 (no) and 1 (yes) for the following: AOD (acute olfactory dysfunction), POD (persistent olfactory dysfunction), NOD (absence of olfactory dysfunction); Covariates: Age, SES [subjective educational and socio-economic status (scale range from 1 to 10 points)], and Vent. Assist. [Ventilatory assistance: not applicable (0), enhanced respiratory support (1) and intubated (2)]. Months = months from diagnosis to assessment. GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

dysfunction. In general, these findings may contribute to further understanding of the neuropsychological and emotional aspects of long-COVID.

Compared to the NOD group of participants, the AOD group presented lower general cognition assessed with MoCA, which included an assessment of short-term memory and working memory, visuospatial abilities and orientation. Objective declarative memory, which is associated with hippocampal function (Squire and Dede, 2015), was not related to the persistence of olfactory dysfunction, and individuals with lower cognitive function had recovered from initial olfactory dysfunction. This is contrary to our hypothesis. We expected an association between the chronicity of olfactory dysfunction in long-COVID patients and cognitive and memory scores, due to a more deleterious effect of the virus on the olfactory system and limbic system regions (Doty, 2022). However, initial symptoms of COVID-19 are very relevant for long-term cognitive alterations. In this sense, recent research has shown that the symptoms during the initial phase of the disease, including olfactory dysfunction, could be determinants to produce brain alterations (Goehringer et al., 2022). Brain hypometabolism correlated with high inflammation and impaired cognition, assessed with MoCA, and was associated with a higher number of symptoms at the time of the initial infection (Goehringer et al., 2022). This hypometabolism affects frontal, insular and temporal cortices, all regions of the olfactory brain network (Guedj et al., 2021; Goehringer et al., 2022). However, this brain hypometabolism of frontal and insular cortices—regions strongly associated with initial olfactory dysfunction (Seubert et al., 2013)—is transient and does not persist over time (Martini et al., 2022). Nevertheless, the hippocampus and the amygdala also presented

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TABLE 7 Multiple regressions predicting immediate ability to recall verbal episodic information (PALIR score), with months since COVID-19 onset, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors.

Predictors	Criterion: PALIR	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
Months,AOD	Age	−0.122	−0.906	0.368	−0.262, 0.098	0.072	−0.010	0.607
	SES	0.01	0.084	0.934	−0.848, 0.922			
	Vent. Assist.	−0.02	−0.164	0.870	−2.990, 2.536			
	Months	−0.216	−1.504	0.137	−0.438, 0.062			
	AOD	−0.269	−0.755	0.453	−16.293, 7.346			
	Months×AOD	0.286	0.779	0.439	−0.347 0.792			
Months,POD	Age	−0.122	−0.946	0.347	−0.256, 0.091	0.129	0.053	3.158
	SES	−0.012	−0.104	0.918	−0.893, 0.804			
	Vent. Assist.	−0.052	−0.434	0.666	−3.288, 2.114			
	Months	−0.063	−0.44	0.661	−0.303, 0.194			
	POD	0.252	0.963	0.339	−3.912, 11.213			
	Months×POD	−0.464	−1.777	0.080	−0.847, 0.049			
Months,NOD	Age	−0.153	−1.132	0.262	−0.285, 0.079	0.096	0.016	0.644
	SES	0.035	0.291	0.772	−0.745, 1.000			
	Vent. Assist.	−0.04	−0.328	0.744	−3.202, 2.299			
	Months	−0.241	−1.361	0.178	−0.519, 0.098			
	NOD	−0.04	−0.138	0.890	−7.866, 6.845			
	Months×NOD	0.237	0.802	0.425	−0.242, 0.568			
GADSA, AOD	Age	−0.162	−1.362	0.178	−0.276, 0.052	0.106	0.028	4.22
	SES	0.027	0.230	0.819	−0.790, 0.996			
	Vent. Assist.	−0.001	−0.006	0.995	−2.784, 2.768			
	GADSA	−0.258	−1.972	0.053	−1.556, 0.009			
	AOD	−0.713	−2.122	0.037	−23.671, −0.730			
	GADSA×AOD	0.674	2.054	0.044	0.051, 3.488			
GADSA, POD	Age	−0.19	−1.525	0.132	−0.303, 0.041	0.058	−0.024	0.001
	SES	−0.008	−0.069	0.945	−0.922, 0.860			
	Vent. Assist.	−0.017	−0.139	0.890	−3.089, 2.686			
	GADSA	−0.105	−0.817	0.417	−1.082, 0.453			
	POD	−0.124	−0.224	0.823	−18.250, 14.564			
	GADSA×POD	0.014	0.025	0.980	−2.190, 2.244			
GADSA, NOD	Age	−0.176	−1.443	0.154	−0.291, 0.047	0.104	0.026	2.763
	SES	0.034	0.286	0.775	−0.760, 1.015			
	Vent. Assist.	−0.004	−0.036	0.971	−2.861, 2.759			
	GADSA	0.136	0.710	0.480	−0.738, 1.554			
	NOD	0.775	1.971	0.053	−0.121, 20.353			
	GADSA×NOD	−0.705	−1.662	0.101	−2.647, 0.241			
GADSD, AOD	Age	−0.177	−1.482	0.143	−0.288, 0.043	0.092	0.013	2.471
	SES	0.011	0.093	0.926	−0.860, 0.944			
	Vent. Assist.	0.018	0.149	0.882	−2.664, 3.093			
	GADSD	−0.259	−1.939	0.057	−1.925, 0.028			
	AOD	−0.606	−1.68	0.097	−22.684, 1.944			
	GADSD×AOD	0.56	1.572	0.121	−0.446, 3.765			

(Continued)

TABLE 7 (Continued)

Predictors	Criterion: PALIR	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
GADSD, POD	Age	−0.182	−1.48	0.143	−0.296, 0.044	0.076	−0.005	0.611
	SES	0.002	0.02	0.984	−0.876, 0.894			
	Vent. Assist.	0.022	0.176	0.861	−2.699, 3.220			
	GADSD	−0.191	−1.426	0.158	−1.679, 0.279			
	POD	−0.487	−0.994	0.323	−21.766, 7.284			
	GADSD×POD	0.391	0.782	0.437	−1.428, 3.268			
GADSD, NOD	Age	−0.188	−1.565	0.122	−0.296, 0.036	0.127	0.051	3.794
	SES	0.034	0.289	0.774	−0.751, 1.005			
	Vent. Assist.	0.026	0.216	0.830	−2.536, 3.151			
	GADSD	0.113	0.615	0.541	−0.931, 1.760			
	NOD	0.913	2.267	0.027	1.430, 22.411			
	GADSD×NOD	−0.855	−1.948	0.056	−3.380, 0.040			
STAIT, AOD	Age	−0.183	−1.491	0.141	−0.296, 0.043	0.048	−0.035	0.853
	SES	−0.013	−0.103	0.919	−0.969, 0.874			
	Vent. Assist.	−0.026	−0.210	0.834	−3.215, 2.603			
	STAIT	−0.014	−0.099	0.921	−0.655, 0.593			
	AOD	−0.200	−0.934	0.353	−10.752, 3.893			
	STAIT×AOD	0.199	0.924	0.359	−0.669, 1.824			
STAIT, POD	Age	−0.205	−1.648	0.104	−0.314, 0.030	0.052	−0.030	0.005
	SES	−0.016	−0.131	0.896	−0.955, 0.837			
	Vent. Assist.	−0.046	−0.363	0.718	−3.474, 2.404			
	STAIT	0.069	0.530	0.598	−0.431, 0.742			
	POD	−0.116	−0.366	0.715	−11.105, 7.659			
	STAIT×POD	−0.024	−0.073	0.942	−1.617, 1.503			
STAIT, NOD	Age	−0.211	−1.701	0.093	−0.318, 0.025	0.063	−0.018	0.512
	SES	0.01	0.084	0.933	−0.870, 0.946			
	Vent. Assist.	−0.039	−0.312	0.756	−3.363, 2.453			
	STAIT	0.155	0.817	0.417	−0.504, 1.203			
	NOD	0.315	1.245	0.217	−2.475, 10.687			
	STAIT×NOD	−0.212	−0.716	0.477	−1.469, 0.693			

The following covariates were included in the analyses: Age, SES and Ventilatory assistance. Significant *p*-values are underlined. *β* shows standardised values. Dichotomisation of the symptoms of olfactory dysfunction is 0 (no) and 1 (yes) for the following: AOD (acute olfactory dysfunction), POD (persistent olfactory dysfunction), NOD (absence of olfactory dysfunction); Covariates: Age, SES [subjective educational and socio-economic status (scale range from 1 to 10 points)], and Vent. Assist. [Ventilatory assistance: not applicable (0), enhanced respiratory support (1) and intubated (2)]. Months = months from diagnosis to assessment. GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

hypermetabolism that was long-lasting (Martini et al., 2022). This more persistent brain dysfunction could be responsible for the persistent cognitive deficits found in patients with recovered olfactory dysfunction. Brain plasticity could account for the different course of evolution of the olfactory symptoms. Brain connectivity of olfactory regions could explain inter-subject differences in the residual olfactory dysfunction found in patients post-infection (Esposito et al., 2022). We note that olfactory dysfunction was self-reported by the participants, and not objectively assessed. Therefore, this finding requires more research, as more studies are needed to elucidate the causes of recovered and persistent olfactory dysfunction and how they interact with cognitive function. The clinical course of olfactory loss after SARS-CoV-2 infection is not entirely understood, and the evidence of the duration and recovery of this symptom is inconsistent across studies (Agyeman et al., 2020; Santos et al., 2021). Studies are being made to elucidate how the initial severity of the dysfunction, viral load, concomitant symptoms, medical history, age, and sex are associated with persistent olfactory dysfunction (Saussez et al., 2021; Sehanobish et al., 2021; Chapurin et al., 2022; Tan et al., 2022). However, these variables are not yet thoroughly studied, and the results are contradictory.

Results revealed that the NOD, AOD, and POD groups were comparable in terms of their depression and anxiety-related symptoms and level of trait-anxiety. Anxiety and depression symptomatology and trait-anxiety were associated with reporting more subjective memory failures after controlling for participants' age, ventilatory assistance, and educational and socio-economic status. However, only depression-related symptoms were associated with general cognitive function or memory when assessed objectively. Depression, followed by negative

TABLE 8 Multiple regressions predicting delayed ability to recall verbal episodic information (PALDR score), with months since COVID-19 onset, symptoms of anxiety and depression, trait-anxiety, and olfactory dysfunction as predictors.

Predictors	Criterion: PALDR	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
Months,AOD	Age	−0.086	−0.665	0.508	−0.076, 0.038	0.140	0.064	0.377
	SES	0.072	0.615	0.540	−0.194, 0.368			
	Vent. Assist.	0.031	0.266	0.791	−0.760, 0.994			
	Months	−0.325	−2.356	0.021	−0.173, −0.014			
	AOD	−0.294	−0.857	0.395	−5.361, 2.140			
	Months×AOD	0.217	0.614	0.541	−0.125, 0.236			
Months,POD	Age	−0.054	−0.428	0.670	−0.068, 0.044	0.160	0.086	2.495
	SES	0.032	0.279	0.781	−0.236, 0.313			
	Vent. Assist.	0.018	0.156	0.876	−0.806, 0.943			
	Months	−0.222	−1.582	0.118	−0.144, 0.017			
	POD	0.318	1.237	0.220	−0.930, 3.966			
	Months×POD	−0.405	−1.580	0.119	−0.260, 0.030			
Months,NOD	Age	−0.085	−0.650	0.518	−0.077, 0.039	0.155	0.081	1.283
	SES	0.069	0.597	0.553	−0.195, 0.361			
	Vent. Assist.	0.019	0.161	0.873	−0.806, 0.947			
	Months	−0.435	−2.542	0.013	−0.223, −0.027			
	NOD	−0.165	−0.590	0.557	−3.037, 1.651			
	Months×NOD	0.324	1.133	0.261	−0.056, 0.202			
GADSA, AOD	Age	−0.189	−1.605	0.113	−0.095, 0.010	0.126	0.050	1.956
	SES	0.100	0.851	0.398	−0.164, 0.408			
	Vent. Assist.	0.031	0.260	0.796	−0.773, 1.004			
	GADSA	−0.256	−1.977	0.052	−0.498, 0.002			
	AOD	−0.657	−1.978	0.052	−7.310, 0.032			
	GADSA×AOD	0.454	1.398	0.166	−0.164, 0.935			
GADSA, POD	Age	−0.189	−1.518	0.134	−0.098, 0.013	0.057	−0.025	0.009
	SES	0.036	0.302	0.764	−0.245, 0.332			
	Vent. Assist.	0.025	0.205	0.838	−0.839, 1.032			
	GADSA	−0.128	−0.996	0.323	−0.373, 0.125			
	POD	0.032	0.057	0.954	−5.163, 5.469			
	GADSA×POD	−0.053	−0.093	0.926	−0.752, 0.685			
GADSA, NOD	Age	−0.204	−1.679	0.098	−0.100, 0.009	0.114	0.037	1.975
	SES	0.085	0.720	0.474	−0.183, 0.389			
	Vent. Assist.	0.018	0.153	0.879	−0.835, 0.974			
	GADSA	0.085	0.446	0.657	−0.286, 0.451			
	NOD	0.716	1.833	0.071	−0.268, 6.320			
	GADSA×NOD	−0.592	−1.405	0.164	−0.792, 0.137			
GADSD, AOD	Age	−0.201	−1.746	0.085	−0.097, 0.006	0.157	0.084	3.233
	SES	0.095	0.822	0.414	−0.165, 0.397			
	Vent. Assist.	0.059	0.492	0.624	−0.676, 1.119			
	GADSD	−0.322	−2.504	0.015	−0.687, −0.078			
	AOD	−0.818	−2.353	0.021	−8.370, −0.689			
	GADSD×AOD	0.617	1.798	0.077	−0.065, 1.249			

(Continued)

TABLE 8 (Continued)

Predictors	Criterion: PALDR	β	*t*	*P*	95% CI	R^2	Adj R^2	*F* change
GADSD, POD	Age	−0.18	−1.466	0.147	−0.095, 0.015	0.080	0.001	0.738
	SES	0.048	0.411	0.682	−0.227, 0.345			
	Vent. Assist.	0.074	0.583	0.562	−0.676, 1.235			
	GADSD	−0.233	−1.742	0.086	−0.592, 0.040			
	POD	−0.432	−0.885	0.379	−6.771, 2.609			
	GADSD×POD	0.428	0.859	0.393	−0.432, 1.085			
GADSD, NOD	Age	−0.208	−1.788	0.078	−0.099, 0.005	0.179	0.108	6.07
	SES	0.09	0.794	0.430	−0.166, 0.385			
	Vent. Assist.	0.062	0.525	0.601	−0.657, 1.127			
	GADSD	0.146	0.818	0.416	−0.249, 0.595			
	NOD	1.125	2.879	0.005	1.460, 8.043			
	GADSD×NOD	−1.048	−2.464	0.016	−1.199, −0.126			
STAIT, AOD	Age	−0.202	−1.691	0.095	−0.099, 0.008	0.093	0.015	1.364
	SES	0.076	0.632	0.530	−0.199, 0.383			
	Vent. Assist.	0.021	0.174	0.862	−0.838, 0.999			
	STAIT	−0.128	−0.95	0.346	−0.291, 0.103			
	AOD	−0.400	−1.912	0.060	−4.530, 0.096			
	STAIT×AOD	0.246	1.168	0.247	−0.163, 0.624			
STAIT, POD	Age	−0.199	−1.590	0.116	−0.100, 0.011	0.045	−0.038	0.337
	SES	0.036	0.302	0.764	−0.247, 0.335			
	Vent. Assist.	0.009	0.070	0.944	−0.921, 0.989			
	STAIT	0.005	0.040	0.968	−0.187, 0.194			
	POD	0.128	0.404	0.687	−2.431, 3.666			
	STAIT×POD	−0.188	−0.581	0.563	−0.655, 0.359	0.082	0.002	0.606
STAIT, NOD	Age	−0.231	−1.877	0.065	−0.107, 0.003			
	SES	0.070	0.583	0.562	−0.206, 0.376			
	Vent. Assist.	0.002	0.014	0.989	−0.925, 0.938			
	STAIT	0.083	0.444	0.658	−0.213, 0.334			
	NOD	0.369	1.474	0.145	−0.551, 3.667			
	STAIT×NOD	−0.229	−0.779	0.439	−0.482, 0.211			

The following covariates were included in the analyses: Age, SES and Ventilatory assistance. Significant *p*-values are underlined. *β* shows standardised values. Dichotomisation of the symptoms of olfactory dysfunction is 0 (no) and 1 (yes) for the following: AOD (acute olfactory dysfunction), POD (persistent olfactory dysfunction), NOD (absence of olfactory dysfunction); Covariates: Age, SES [subjective educational and socio-economic status (scale range from 1 to 10 points)], and Vent. Assist. [Ventilatory assistance: not applicable (0), enhanced respiratory support (1) and intubated (2)]. Months = months from diagnosis to assessment. GADSA = Anxiety subscale of the Goldberg Anxiety and Depression Scale; GADSD = Depression subscale of the Goldberg Anxiety and Depression Scale; STAIT = Trait-Anxiety subscale of the State–Trait Anxiety Inventory.

affect, such as higher levels of distress and anxiety, were the factors most highly related to memory complaints at all ages in normal population (Ponds et al., 1997; Clarnette et al., 2001; Reid and MacLullich, 2006; Zullo et al., 2021). Studies in long-COVID patients indicate a relationship between mood disorders and memory performance or complaints and persistent olfactory symptoms. However, these studies presented differences with our study. In the study of Voruz et al. (2022), subgroups of long-COVID patients, with a higher representation of males than in the present study, were made according to the severity of the acute illness, and a high prevalence of psychiatric symptoms and cognitive deficits were found regardless of the severity when compared to normative population. Long-term episodic memory assessed by Buschke test was impaired in the group with severe-acute symptoms and positively correlated with emotional apathy, but not with anxiety and depression. In this study, Voruz et al. (2022) objectively assessed persistent olfactory dysfunction using an olfaction test. In the group of patients with moderate olfactory symptoms, the olfactory dysfunction was associated with a diminished ability to recognise emotions, but not with memory function (Voruz et al., 2022). In addition, the study of Delgado-Alonso et al. (2022), which also used an objective measure of olfactory dysfunction, found an association between persistent olfactory dysfunction and delayed visual memory in a sample with a sex and age distribution comparable to the sample of our study. They also found that trait-anxiety moderately correlated with delayed verbal memory performance, and depression was not associated with objective cognitive scores. When assessing subjective memory complaints, neuropsychiatric scores were more relevant and, in agreement with our results, memory complaints were clearly associated with anxiety and depression in

long-COVID participants (Almeria et al., 2020; Titze de Almeida et al., 2022). Interestingly, Almeria et al. (2020) also found an association of anosmia as an acute symptom non-objectively assessed with the working memory scores included in our assessment of cognition but not with delayed memory performance, as we found.

Olfactory dysfunction and older age are relevant predictors for the development of long-COVID (Brechbühl et al., 2021; Sudre et al., 2021). In our study we included participants' age as covariate in regression models. Our participants' age was below 65 years, so our sample is not aged. The association between age and better self-reported memory function during communication in studies using older samples of long-COVID patients than ours could be interpreted as impaired metacognition (Voruz et al., 2022). For this reason, it is important to consider age as a control variable in studies comparing subjective and objective memory performance in this population.

Self-report of memory by questionnaires offers an easily administered means of assessing the incidence of a range of memory failures and has been used in normal subjects (Papaliagkas et al., 2017) and patients suffering neurological diseases (Geffen et al., 1991). The MFE not only asked participants to recall instances of different forms of memory failure but also to rate the frequency with which they had occurred. This provides a more valid self-report than other methods, demanding more memory during their completion (Sunderland et al., 1984). However, based on regression analyses, self-reported memory failures are associated with depressive symptomatology, especially in long-COVID patients with no experience of olfactory dysfunction.

4.1. Limitations of the current study

This study presents several limitations. Firstly, we recruited voluntary participants. Therefore, moderately or slightly affected subjects were more prone to accept enrolment in the study. To some extent, this may influence our ability to generalise the findings to the total population with this syndrome, which includes subjects with severe long-COVID symptoms. Secondly, olfactory dysfunction, as well as other long-COVID symptoms, were evaluated 3–30 months after the acute phase of the COVID-19 infection by a subjective retrospective report. This method of assessment of olfactory dysfunction was also used in studies that included self-reported questionnaires to collect olfactory symptoms several months after the acute infection (Almeria et al., 2020; Helmsdal et al., 2022; Seeßle et al., 2022). However, the description of olfactory dysfunction was not provided by a standardised objective protocol and did not include an index of the severity of olfactory dysfunction. This report may be influenced not only by individuals' subjective perception but also by memory function when reporting the presence of olfactory dysfunction at the acute phase of the infection. This limitation also applies to other reported symptoms at the time of assessment, which were not objectively assessed. Thirdly, we ignored participants' pre-COVID memory cognitive and emotional state, so we cannot draw definite conclusions about a causal relationship between olfactory dysfunction and cognition. Finally, the questionnaire used to assess subjective memory function involves components of declarative episodic memory, working memory, language, attention, planning, and intentionality. The items of this questionnaire measure processes of recognition and recall of visual, verbal, and spatial information, prospective and retrospective memory, and executive control functions (Montejo et al., 2014). However, attention and executive function were not directly assessed by subjective questionnaires or objective tests in this study. We were mainly focused on declarative memory, as previous research has also found that this function is impaired in long-COVID patients (Damiano et al., 2022; Delgado-Alonso et al., 2022; Voruz et al., 2022; Llana et al., 2022b). However, attention and executive function are also significant processes affected in long-COVID patients (Delgado-Alonso et al., 2022).

5. Conclusion

The research shows that it is relevant to distinguish between participants on the basis of their olfactory dysfunction after SARS-CoV-2 infection. Olfactory dysfunction in the acute phase of the infection by COVID-19 is related to cognitive deficits in objective tests, and mood disturbances are associated with self-reported and objective memory. These findings may contribute to further understanding the neuropsychological and emotional aspects of long-COVID.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comité de ética en investigación Universitat Politècnica de València. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM-L, MM and M-CJ conceived and planned the experiments. M-CJ acquired the funding and administrated the project. MM-L, MM, TL and SG-A carried out the experiments. MM-L, SG-A and TL contributed to the creation of the database. MM-L analysed the data. SG-A designed the graphic representation. MM, MM-L, VH, M-CJ and TL drafted the manuscript. All authors reviewed the manuscript, contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1076743/full#supplementary-material

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Olfactory dysfunction: A plausible source of COVID-19-induced neuropsychiatric symptoms

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Olfactory dysfunction and neuropsychiatric symptoms are commonly reported by patients of coronavirus disease 2019 (COVID-19), a respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Evidence from recent research suggests linkages between altered or loss of smell and neuropsychiatric symptoms after infection with the coronavirus. Systemic inflammation and ischemic injury are believed to be the major cause of COVID-19-related CNS manifestation. Yet, some evidence suggest a neurotropic property of SARS-CoV-2. This mini-review article summarizes the neural correlates of olfaction and discusses the potential of *trans*-neuronal transmission of SARS-CoV-2 or its particles within the olfactory connections in the brain. The impact of the dysfunction in the olfactory network on the neuropsychiatric symptoms associated with COVID-19 will also be discussed.

KEYWORDS

COVID-19, neuropsychiatric symptoms, nervus terminalis, olfactory system, *trans*-neuronal viral transmission

1. Introduction

Coronavirus Disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since its outbreak in 2019, over 650 million confirmed cases were reported globally (World Health Organization, 2023). The commonly reported symptoms included cough, fever, fatigue, loss of taste or smell, sore throat, headache, aches, diarrhea, rash on skin, red or irritated eyes, and shortness of breath (World Health Organization, 2023). Emerging evidence reports the impact of COVID-19 on influencing taste and smell, not only in the acute phase but also extending to the recovery phase. Previous literature hypothesized that such dysfunction could be related to the influence of SARS-CoV-2 *via* its binding to angiotensin-converting enzyme-2 (ACE2) receptors, an entry protein for SARS-CoV-2 (Zhou et al., 2020), on mucous membranes, primarily in the olfactory epithelia (Bourgonje et al., 2020). The surface expression of ACE2 protein was reported to be more remarkable in lung alveolar epithelial cells and enterocytes of small intestine (Hamming et al., 2004). The inhaled virus binds to the ACE2 receptors in epithelial cells in the nasal

cavity and further propagates to the respiratory tract (Mason, 2020). The expression of SARS-CoV-2 entry protein ACE2 in airway epithelial cells was found to be increased 3 times in patients with COVID-19 (Chua et al., 2020). Infected epithelial cells secrete chemokines that trigger the migration of different immune cell populations including neutrophils, T cells and mast cells to the site and cause further damage to the epithelium. Analysis of RNA-seq further demonstrated that type II alveolar cells, myocardial cells, proximal tubule cells of kidney, ileum and esophagus epithelial cells and urothelial cells of bladder were vulnerable to the manifestation of different organ infections or damage (Zou et al., 2020) which supports the potential impacts of SARS-CoV-2. Torabi et al. (2020) reported that COVID-19 patients had significantly elevated Tumor necrosis factor α (TNF-α) levels in the olfactory epithelium, which may induce direct inflammation and contribute to the acute olfactory loss described in many COVID-19 patients. Other than invading through ACE2 receptors, it is hypothesized that viral invasion could access the central nervous system (CNS) through a hematogenous route [blood brain barrier (BBB)], neuronal retrograde dissemination route (peripheral neurons) or transcribial routes [olfactory bulb or cerebral spinal fluid (CSF) (Baig and Sanders, 2020]. Being determined by the infection of SARS-CoV-2, COVID-19 is a multi-systemic disease. Different systems like respiratory, cardiovascular, nervous, renal, and digestive systems are involved in the disease. Multiple signs and symptoms, including widespread inflammatory response, cytokine storm, and abnormalities of blood cells, are possible in COVID-19. Due to the hyperinflammation and other abnormalities, the nervous system may be affected (Temgoua et al., 2020). In this review, details of how COVID-19 influences olfactory function and its associated mechanistic pathways in damaging the CNS will be discussed.

2. Olfaction and its neural correlates

Olfaction is one of the critical senses for humans to interact with the world. In the olfactory system, olfactory stimuli are received by first-order sensory neurons embedded in the olfactory epithelium located in the upper side of the nasal cavity, which then pass information to the olfactory bulb in the brain at the base of the frontal lobe (Firestein, 2001; Shipley et al., 2003; Doty, 2009). The olfactory bulb is a vital intermediate relay station of the olfactory pathway, which passes the olfactory information to the brain. The olfactory bulb projects information to the primary olfactory cortex *via* the olfactory tract, which is formed by the fibers from the output neurons, namely mitral and tufted cell axons (Shipley et al., 2003; Doty, 2009; Zhou et al., 2019). The primary olfactory area consists of numerous cortical and subcortical regions of the brain, including the anterior olfactory nucleus, the piriform cortex (posterior orbitofrontal cortex; stocktickerOFC), parts of the amygdala, the olfactory tubercle, the frontal and temporal piriform cortices, etc. (Doty, 2009; Zhou et al., 2019; Cersosimo et al., 2021). The primary olfactory cortex directly projects information to the secondary olfactory regions, which include the thalamus, hypothalamus, hippocampus, and stocktickerOFC (Doty, 2009; Zhou et al., 2019; Cersosimo et al., 2021).

3. Olfactory dysfunction

Olfactory dysfunction can be a total loss of smell (anosmia), an incomplete loss of smell (partial anosmia, hyposmia, or microsmia), and distortion of smell (dysosmia), a presence of a scent without stimulus (phantosmias); the inability to recognize odors (olfactory agnosia) (Doty, 2009; Han et al., 2019). OD can be bilateral or unilateral (Doty, 2009); thus, some individuals with unilateral OD may not be aware and diagnosed immediately. Around 29% of the population suffers from OD (Desiato et al., 2021), in which older men have the highest prevalence (>55 years; 34.5%) (Desiato et al., 2021). Besides age, upper respiratory infections, brain trauma, and sinonasal disease can also cause olfactory loss (Temmel et al., 2002; Doty, 2009). Neurological disorders are also a common cause of OD (Doty, 2009; Han et al., 2019). Most recently, COVID-19 is also found to be related to OD (Whitcroft and Hummel, 2020).

Olfactory dysfunction is usually associated with structural and functional changes of the brain. The volume of the olfactory bulb is positively correlated with the olfactory function, supported by a large body of research (Yousem et al., 1998; Rombaux et al., 2006; Buschhüter et al., 2008; Seubert et al., 2013; Mazal et al., 2016; Han et al., 2018). A decrease in the gray matter volume was also reported across the primary and the secondary olfactory cortex in individuals suffering from OD compared to healthy controls (Han et al., 2018, 2019). One of the explanations for these structural changes is the decreased sensory input due to olfactory loss (Bitter et al., 2010). Reduction in white matter connectivity in olfactory brain regions (Ibarretxe-Bilbao et al., 2010; Erb et al., 2012; Erb-Eigner et al., 2014) and between the corpus callosum and the superior longitudinal fasciculi (Segura et al., 2013) was also associated with OD. A reduction of fiber connections in different areas of the brain could be reflecting a common cause of degeneration, like aging or other degenerative illness, which are highly related to OD (Segura et al., 2013).

The functional changes of the brain under OD can be classified into three types (Han et al., 2019). First, a widespread decrease in activation among olfactory-related brain regions, including the piriform cortex, amygdala, OFC, insula, and anterior cingulate cortex (Levy et al., 1998, 1999; Pellegrino et al., 2016; Han et al., 2018; Moon et al., 2018) was found in OD patients. These regions are responsible for encoding information (e.g., smell), cognitive-emotional processing, decision-making, and attention allocation. Second, top-down cognitive modulation moderates olfactory perception by higher levels of cognitive processing (Rolls, 2011), such as olfactory imagery, odor expectation, and odor-related words. Individuals with OD were found to be allocating more resources for odor imagery, resulting in a higher activation level in the dorsal lateral prefrontal cortex, cerebellum, and precuneus (Flohr et al., 2014). Similarly, higher activation was found in the left inferior frontal gyrus, insula, and bilateral angular gyrus for individuals with OD while expecting odor-related words (Han et al., 2020). Lastly, the change in the functional network is also found to be related to OD. Functional connectivity measured the temporal correlation of neuronal activity between different brain regions (Damoiseaux et al., 2006). A widespread reduction in functional connectivity in olfactory and non-olfactory networks has been found among individuals with OD (Murphy et al.,

2005; Nigri et al., 2013; Kollndorfer et al., 2015; Su et al., 2015; Yoneyama et al., 2018). For example, reduced connectivity in the somatosensory and integrative networks was found in people with OD (Kollndorfer et al., 2015), which affects the performance and coordination of motor tasks as well as sensory integration processes. Connectivity between the regions in the olfactory brain areas like the anterior cingulate cortex, the entorhinal cortex, and the cerebellum were also found to be reduced among patients with OD (Kollndorfer et al., 2015; Su et al., 2015).

Being connected to multiple cortical and subcortical regions of the brain, the dysfunction of the olfactory system is related to several mental health problems, including schizophrenia, depression, and an early clinical sign of Alzheimer's disease and Parkinson's disease (Moberg et al., 1999; Doty, 2009; Yuan and Slotnick, 2014). With a 29% prevalence rate of OD (Desiato et al., 2021), its impact on neuropsychiatric diseases cannot be ignored. To better diagnose and rehabilitate patients with OD, the cause of it should be clearly identified. One of the common causes of OD discovered recently is due to the infection with SARS-CoV-2.

4. COVID-19-induced OD and neuropsychiatric symptoms

With the recent COVID-19 outbreak, the number of patients with OD increased. Based on a meta-analysis published in 2020, the prevalence rate for OD in COVID-19 patients was 43% (von Bartheld et al., 2020), which dropped globally to about one-tenth with the more recent Omicron variants of COVID-19 (von Bartheld and Wang, 2023). Some COVID-19 patients have long-lasting OD (Moein et al., 2020; Boscolo-Rizzo et al., 2022; Tan et al., 2022). Infection with SARS-CoV-2 could affect the olfactory bulb and other olfaction-related brain regions. The average volume of the olfactory bulb and tract was significantly reduced in COVID-19 patients compared with the control (Altunisik et al., 2021; Yildirim et al., 2022). Douaud et al. (2022) found that the gray matter thickness of the OFC and the parahippocampal gyrus decreased among COVID-19 cases, which echoes the histological findings that ischemic injury was observed through the hippocampal CA1 region and the surrounding parahippocampal region (Fabbri et al., 2021).

Coronavirus disease 2019 patients suffering from OD are more likely to develop psychological disabilities, when compared with patients without OD. In an online survey, among 322 COVID-19 cases experiencing OD, 43% also experienced depression (Coelho et al., 2021). Another study reported that COVID-19 patients who experienced OD had 30% more risk for suicidal thoughts and depression compared with those without OD (Yom-Tov et al., 2021). Higher anxiety scores were also reported from COVID-19 patients who experienced OD (Dudine et al., 2021). These findings indicate the association among COVID-19, OD and neuropsychiatric symptoms. The plausible ways of how SARS-CoV-2 could damage the CNS and result in neuropsychiatric manifestations will be discussed below.

5. CNS consequences of COVID-19

Growing evidence supports that SARS-CoV-2 can damage the CNS. Neuroinflammation, activation of microglia and neuronal death were found in postmortem cortex tissues of COVID-19 patients, and hyperemia of the meninges was observed in 90% of patients in an autopsy study (Boroujeni et al., 2021; Colombo et al., 2021). Mild neuropathological changes in formalin-fixed postmortem samples of COVID-19 patients, and pronounced neuroinflammatory changes in the brainstem suggested that the CNS damage was not directly caused by SARS-CoV-2 (Matschke et al., 2020). In animal studies using Syrian hamsters and non-human primates as models, the detection of SARS-CoV-2 viral particles in the olfactory pathway was associated with robust neuroinflammation and neuronal damage (Beckman et al., 2022; Käufer et al., 2022). Neuroinflammation could be sustained for a long period of time even after the acute phase of the disease. In fact, long-term deficits in olfactory function and neuropsychiatric deficits are observed in a significant proportion of individuals who recovered from COVID-19 (Badenoch et al., 2021; Doty, 2022). Such manifestations of multi-system symptoms after recovery from COVID-19 are termed "long-COVID" (Stefanou et al., 2022). More than one-third of patients reported long-COVID symptoms related to the nervous system (Stefanou et al., 2022), which includes fatigue, "brain fog," cognitive dysfunction, alteration in gustation/olfaction and psychiatric manifestation like mood disturbances (Premraj et al., 2022; Stefanou et al., 2022). Persistent systemic inflammation and the presence of viral RNA in the brain of COVID-19 patients after a prolonged period are considered a plausible cause of long-COVID manifestation of neuropsychiatric symptoms (Stein et al., 2022). Nevertheless, there are different hypotheses suggesting the routes of entry to the CNS. For instance, SARS-CoV-2 was suggested to enter the brain through invasion of enterocytes of the gut where direct connection of the enteric nervous system with the brain are made *via* the vagus nerve (Gao et al., 2020). Nagu et al. (2020) proposed another route that is commonly adopted by other viruses including coronavirus, which is by infecting the leukocytes for transporting the virus across the BBB, triggering the release of proinflammatory cytokines and chemokines that increases the permeability of BBB, hence facilitating the entry of SARS-CoV-2 to the CNS and causing damage. The olfactory bulb and neurons were proposed to be an important site for SARS-CoV-2-induced CNS damage (Wu et al., 2020). All these paths involve the binding of the spike protein from the coronavirus to the ACE2 receptor on the target cells, which is abundantly expressed on various cell types including nerve cells (Iroegbu et al., 2020). Due to the vicinity of the olfactory bulb and neurons with the brain, it was believed that the olfactory bulb could be the first site of neuroinvasion by SARS-CoV-2. However, existing evidence has questioned this claim.

6. Routes of viral invasion

Although the olfactory bulb has direct neural connection to the olfactory sensory epithelium in the nasal cavity (Meinhardt et al., 2021; Xydakis et al., 2021; Lopez et al., 2022), neuroinvasion associated with SARS-CoV-2 is less likely to be initiated through

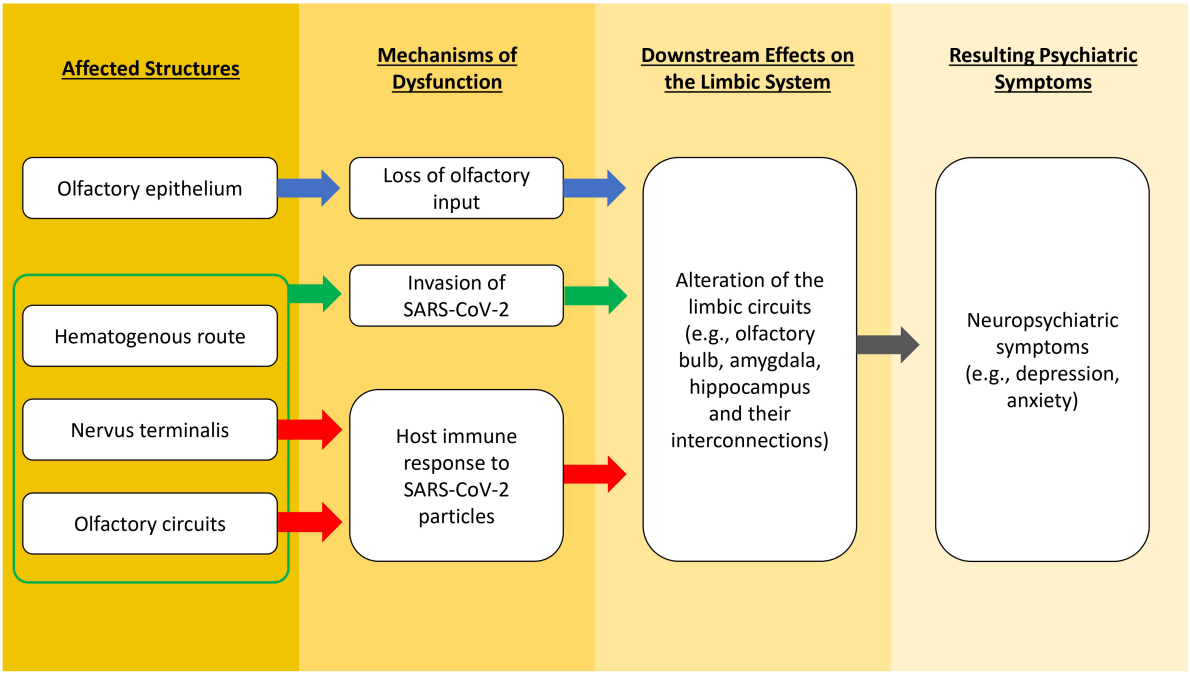

FIGURE 1
A flowchart illustrating different possible mechanisms that lead to altered functions of the limbic system and the associated neuropsychiatric symptoms in COVID-19.

infection at the olfactory bulb. In the olfactory mucosa, ACE2 and neuropilin-1 are highly expressed, providing cellular access points for SARS-CoV-2 (Butowt and Bilinska, 2020; Cantuti-Castelvetri et al., 2020). In contrast, ACE2 is not expressed in olfactory receptor neurons, making them less likely to be infected with SARS-CoV-2 (Butowt et al., 2021; Khan et al., 2021). Furthermore, although SARS-CoV-2 RNA was detected in the olfactory bulb in postmortem COVID-19 brain tissues (Lopez et al., 2022; Serrano et al., 2022), the samples always included the nervus terminalis neurons that express ACE2 (Bilinska et al., 2021; Butowt and von Bartheld, 2022). Without removal of the nervus terminalis from the olfactory bulb, it cannot be differentiated whether the olfactory bulb or the nervus terminalis is infected by the virus based on the RNA data. Furthermore, infection of the olfactory sensory neurons, and the parenchyma of the olfactory bulb by live SARS-CoV-2 was not supported by other evidence (Khan et al., 2021). Reduced volume of the olfactory bulb and tract in COVID-19 patients could be explained by infection of the olfactory epithelium, eliminating crucial support functions performed by the sustentacular cells and the Bowman gland cells, and causing inflammatory or immune reactions in the olfactory epithelium to the olfactory bulb (Liang and Wang, 2021). The death of the infected support cells in the olfactory epithelium is likely to be the cause of OD in COVID-19 instead of the neuroinvasion of the olfactory bulb (Butowt et al., 2023). Taken together, the idea that the olfactory bulb is an important site of neuroinvasion caused by SARS-CoV-2 is unlikely and, at best, highly controversial.

Alternatively, the nervus terminalis may be considered another path for SARS-CoV-2-induced OD and neural damage *via trans*-synaptic transmission mechanism (Gandhi et al., 2020). The nervus terminalis (or terminal nerve) is closely positioned next to the olfactory nerve, which are located on the anterior and ventromedial surface of the olfactory bulb (Sonne et al., 2017), and this is where the evidence for the presence of SARS-CoV-2 RNA is found (Khan et al., 2021; de Melo et al., 2022). The nervus terminalis neurons express ACE2, which allows the binding of the spike protein from SARS-CoV-2 (Bilinska et al., 2021; Butowt and von Bartheld, 2022). Furthermore, the nervus terminalis projects fibers to the nasal mucosa as well as to the limbic network in the brain, which may provide a direct path for the virus from the neuroepithelium to the CNS (Wirsig-Wiechmann and Lepri, 1991). Abnormalities in limbic areas (e.g., amygdala and entorhinal cortex) are related to depression and anxiety (Charney and Deutch, 1996). Based on these facts, we suggest a novel possibility of CNS manifestation of COVID-19 through the primary attack on the nervus terminalis. Nevertheless, contradictory results from RNA analysis of cerebrospinal fluid in living COVID-19 patients with neuropsychiatric manifestations were reported in another study (Spudich and Nath, 2022), which challenges the neurotropism hypothesis of SARS-CoV-2. Furthermore, neuropathological and autopsy studies show conflicting results in neurotropism of SARS-CoV-2. Some research teams detected viral RNA in the olfactory mucosa, olfactory bulb, olfactory tubercle and other brain regions of COVID-19 patients, and viral proteins in cranial nerves and brainstem (Matschke et al., 2020; Meinhardt et al., 2021), which is observed simultaneously with hyperinflammation in the olfactory bulb and other regions like brainstem. Other teams, however, could not detect the presence of viral RNA or proteins in postmortem brain samples nor specific brain changes related to the virus (Solomon et al., 2020; Fullard et al., 2021). Though neurological manifestations are common in COVID-19 patients,

it remains a debate whether SARS-CoV-2 damages the CNS *via* neurotropism, systemic inflammation (Emmi et al., 2023), or both. The abovementioned possible mechanisms that lead to altered functions of the limbic system and the associated neuropsychiatric symptoms in COVID-19 are illustrated in **Figure 1**.

7. Conclusion

In this review, we discussed the possible mechanisms of how SARS-CoV-2 may cause neuropsychiatric symptoms. We speculate SARS-CoV-2 or its particles could attack the nervus terminalis rather than the olfactory pathways and invade other brain regions connected to it through *trans*-synaptic transmission mechanism, which may be a potential cause for the neuropsychiatric symptoms of COVID-19. As an alternative, viral particles may elicit host immune responses, or lack of olfactory input may alter limbic circuits connected to the olfactory system, thereby altering limbic structures which manifest in neuropsychiatric symptoms. COVID-19 is regarded as a multi-systemic disease which may also cause CNS disruption *via* cytokine storm, hyperinflammation, vascular dysfunction and abnormal blood physiology. Ischemic injury remains a major cause of cortical damage and olfactory dysfunction based on our current understanding. Future research is required to elucidate the precise mechanisms by which SARS-CoV-2 causes dysfunction in limbic circuits that manifest as neuropsychiatric symptoms.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Exploring the research landscape of COVID-19-induced olfactory dysfunction: A bibliometric study

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Since the outbreak of COVID-19, olfactory dysfunction (OD) has become an important and persistent legacy problem that seriously affects the quality of life. The purpose of this paper is to quantitatively analyze and visualize the current research status and development trend of COVID-19 related OD by using VOSviewer software. Based on the Web of Science database, a total of 1,592 relevant documents were retrieved in January 2023, with publication time spanning from 2020 to 2023. The bibliometric analysis revealed that the most influential research results in the field of COVID-19 related OD were concentrated in journals of related disciplines such as otorhinolaryngology, medicine, general and internal, virology, neurosciences, etc. The knowledge base of the research is mainly formed in two fields: COVID-19 clinical research and OD specialized research. The research hotspots are mainly concentrated in six directions: COVID-19, long COVID, smell, anosmia, OD, and recovery. Based on the results of the bibliometric analysis, the temporal trends of COVID-19 related OD studies were visually revealed, and relevant suggestions for future research were proposed.

KEYWORDS

COVID-19 pandemic, long COVID, olfactory dysfunction, co-citation analysis, co-word analysis, cluster analysis

1. Introduction

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in late 2019 and quickly spread globally, leading to the declaration of a pandemic by the World Health Organization on March 11, 2020 (Sharma et al., 2020). A growing body of evidence suggests that the most common symptom of COVID-19 infection is the loss or diminished sense of smell (hyposmia) (Gori et al., 2020; Dawson et al., 2021; de Melo et al., 2021; Gupta et al., 2021). Before the COVID-19 pandemic, other factors such as viral infections, sinus disease, and head trauma could also cause olfactory loss (Desai and Oppenheimer, 2021). However, SARS-CoV-2 has been found to cause a more severe form of hyposmia compared to other seasonal cold viruses (Haehner et al., 2022). OD is also one of the most common neurological complications reported among patients with COVID-19 (Azizi and Azizi, 2020; Wei et al., 2022).

OD associated with COVID-19 has a significant impact on quality of life and may lead to several negative outcomes, such as malnutrition, weight loss, food poisoning, and exposure to hazardous chemicals (Gómez-Iglesias et al., 2020; Glezer et al., 2021). Moreover, individuals with COVID-19 who experience olfactory loss are more likely to suffer from poor

TABLE 1 The status of literature publications (2020–2023).

Publication year	Articles	Review articles	Count
2020	278	113	391
2021	510	144	654
2022	430	101	51
2023	4	1	5
Total	1,222 (76.76%)	359 (22.55%)	1,581 (99.31%)

sleep quality, high levels of fatigue, and depression compared to those who do not (Alqahtani et al., 2022).

In response to the COVID-19 pandemic, many researchers have focused on studying OD. Several literature reviews, systematic reviews, and meta-analyses have been conducted, including a meta-analysis of data from 24 studies of 8,438 patients with COVID-19 from 13 countries (Agyeman et al., 2020) and a meta-analysis of 11,074 patients with confirmed COVID-19 in 51 studies (Aziz et al., 2021). These studies have shown that OD is a common and important extrapulmonary manifestation of COVID-19.

However, despite these efforts, there have been only a limited number of comprehensive, quantitative analyses, and visualizations of COVID-19 related OD using bibliometrics. The data from these analyses were collected before 2021 (Hu et al., 2022; Zyoud et al., 2022), making it challenging to identify the most recent research directions in this field. To address this gap, this study will perform a comprehensive review and visualization of existing COVID-19 related OD research using a bibliometric approach. Specifically, co-citation analysis, co-word analysis, and cluster analysis will be applied to data retrieved from the Web of Science using VOSviewer. The results of this analysis will identify the knowledge base and research hotspots of COVID-19 related OD, reveal the temporal trends of this research, and provide recommendations for future COVID-19 related OD research.

2. Data source and analysis method

2.1. Data source

To ensure the authority and comprehensiveness of the study data, the Web of Science Core Collection was used as the data source, from which the Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) databases. The search terms for the COVID-19 Pandemic included "COVID-19," "Corona Virus," "Coronavirus," and "2019-nCoV." The search terms for Olfaction research included "olfactory," "olfaction," and "smell." The search query was set as "TS = (COVID-19 or Corona Virus or Coronavirus or 2019-nCoV) AND TS = (olfactory or olfaction or smell)." The types of literature were limited to articles, review articles, and early access, with a publication year restricted to 2020 to present. The search was conducted on January 23, 2023, and a total of 1,592 relevant literature was finally retrieved and used as the data source for this study.

Table 1 presents the number of papers investigating OD in the context of the COVID-19 pandemic. As of January 23, 2023, 391 papers were published in 2020, with 655 papers in 2021, 541 papers in 2022, and 5 papers having been published in 2023. In the 1,592 relevant literature, there were 1,222 articles (76.76%), 359 review articles (22.55%), and 11 papers in early access type (0.69%). This indicates a significant amount of in-depth studies on COVID-19 related OD have been conducted since 2020, and suggests the rapidly evolving nature of the COVID-19 pandemic has necessitated a large number of Review Articles to keep up with the latest literature data.

According to Table 2, the top 10 countries or regions involved in COVID-19 related research are highly concentrated. Out of the 104 countries or regions worldwide, the United States leads with a total of 395 documents, representing 24.812% of the scientific output. This is followed by Italy with 216 articles, accounting for 13.568%. Other countries such as England, Germany, France, and others have also made significant contributions to the research output. The top 10 countries alone make up 93.72% of the total publications on the subject, highlighting a noticeable concentration trend.

2.2. Analysis method

Since 1969 (Pritchard, 1969), bibliometric analysis has been widely used in scientific and application fields (Ellegaard and Wallin, 2015; Huang et al., 2016; Xu et al., 2021). Since 2020, bibliometric analysis has been used (Zhang et al., 2020; Lin et al., 2022; Pang et al., 2022; Xie et al., 2022) to help researchers grasp the knowledge base, hot spots, and trends in the research field of COVID-19. VOSviewer, a powerful bibliometric analysis software developed by van Eck and Waltman in 2010, which offers advanced graphical representation capabilities for mapping knowledge units and their relationships within the research literature (van Eck and Waltman, 2010). In order to perform bibliometric analysis of the knowledge base and research hotspots of COVID-19 related OD research, VOSviewer was used as the knowledge mapping analysis tool in this paper, and the software version was VOSviewer_1.6.19. First, the full record and cited references data of the retrieved 1,592 literature references data retrieved were imported into VOSviewer, and then co-citation analysis, co-word analysis and cluster analysis were performed. The research structure of this review is shown in Figure 1.

3. Results

3.1. Most co-cited journals

As depicted in Figure 2, the results of the co-citation analysis of cited sources are presented in a mapping format, produced using the VOSviewer software. In order to ensure the relevance of the results, the authors chose to only include cited sources with a citation frequency exceeding 200. Out of the 91 cited sources present in the data set, 61 sources met this criterion.

The visual representation in Figure 2 utilizes nodes to symbolize sources and links to indicate the co-citation relationships between them. Sources that share close co-citation relationships are marked with the same color. The results of the analysis highlight

TABLE 2 The geographical distribution (Top 10).

Country/region	Count	Percentage	Country/region	Count	Percentage
USA	395	24.812	Turkey	108	6.784
Italy	216	13.568	Peoples R China	99	6.219
England	164	10.302	Spain	88	5.528
Germany	138	8.668	India	79	4.962
France	133	8.354	Belgium	72	4.523

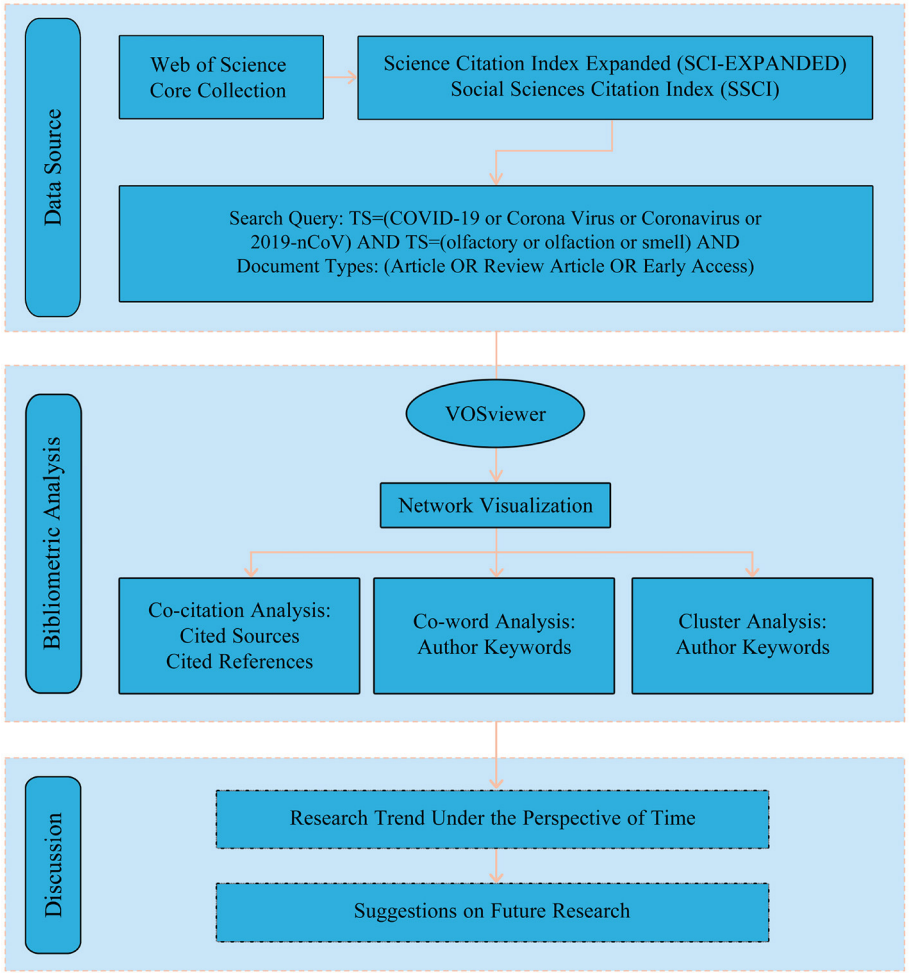

FIGURE 1
The structure of this review.

that the majority of the co-cited sources in COVID-19 related ocular disease research are journal articles. Notable journals such as the *New England Journal of Medicine*, *European Archives of Oto-Rhino-Laryngology*, *Lancet*, and *Nature* occupy a central position and are closely distributed, showcasing their significant influence on the topic of COVID-19 related ocular disease research and their interrelatedness.

Table 3 showcases the top ten journals as determined by the Total Link Strength (TLS) metric in VOSviewer. The *New England Journal of Medicine*, *European Archives of Oto-Rhino-Laryngology*, and *International Forum of Allergy & Rhinology* stand out as the journals with higher Local Citation Score (LCS) and TLS values compared to other journals. This implies that these journals possess a strong reputation in the field of COVID-19 related ocular disease research. Eight of the top ten journals are published in the United States while the remaining two are published in Europe, indicating a concentration of COVID-19 related ocular disease research in these regions. The analysis results in Table 3 also reveal that the most impactful journals for COVID-19 related ocular disease research primarily belong to the categories of otorhinolaryngology, medicine, general and internal medicine, virology, and neurosciences.

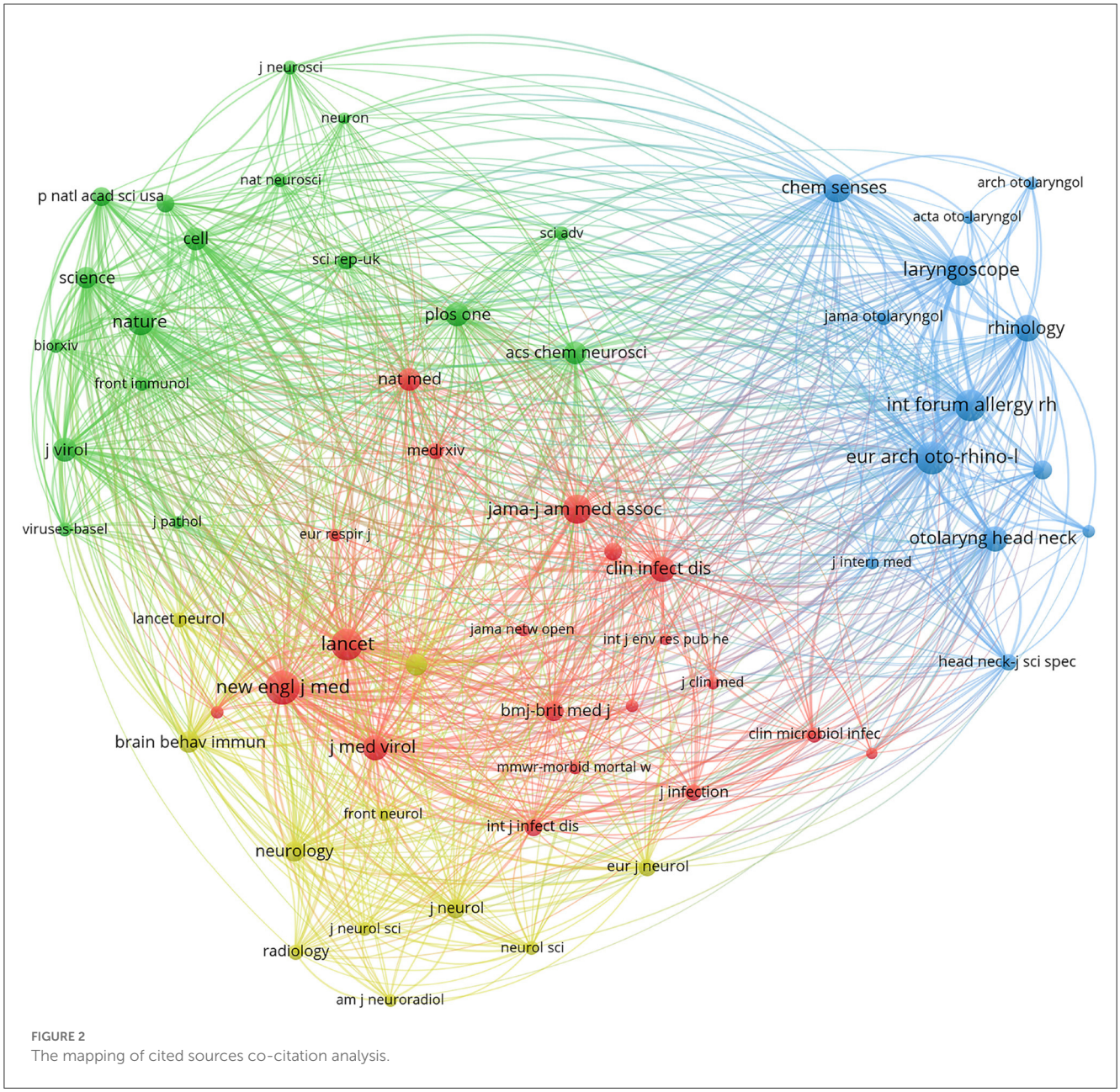

FIGURE 2
The mapping of cited sources co-citation analysis.

Figure 2 visually represents the co-citation relationships among the most influential journals in COVID-19 related OD research. The analysis highlights the dominance of medicine, general, and internal journals (e.g., *New England Journal of Medicine*, *Lancet*) in the red area, while the blue area is dominated by otorhinolaryngology journals (e.g., *European Archives of Oto-Rhino-Laryngology*, *International Forum of Allergy & Rhinology*). The yellow area is a cluster of neurology journals, including *Frontiers in Neurology*, and the green area is dominated by comprehensive journals such as *Nature* and *Science*. This illustration demonstrates a pronounced interdisciplinary cross-fertilization among COVID-19 related OD research themes, as evidenced by the co-citation relationships among journals in the red, blue, yellow, and green regions.

3.2. Most co-cited references

As depicted in Figure 3, the results of the co-citation analysis of highly cited references are presented, with the 20 most frequently cited references highlighted. The selection criteria of these references were established based on a minimum citation frequency of 128, out of a total of 40,340 cited references in the dataset. These highly cited references serve as indicators of the key topics and influential works in the field.

Figure 3 and Table 4 present the results of the highly cited reference analysis in the COVID-19 related OD research field. The selection criteria for these cited references were a citation frequency of over 128, and 20 references met this criterion among the 40,340 cited references in the dataset. The results are sorted by the TLS metric, and the LCS and Global Citation Score (GCS) are also listed.

TABLE 3 Highly total link strength cited journals (Top 10).

Journal	JCR category	Country of publisher	LCS	TLS
New England journal of medicine	GIM	USA	1,611	45,004
European archives of Oto-Rhino-Laryngology	ORL	USA	1,418	39,503
International forum of allergy rhinology	ORL	USA	1,335	37,517
Lancet	GIM	USA	1,326	35,443
Laryngoscope	MRE/ORL	USA	1,250	34,712
Nature	MS	Germany	1,001	34,552
Chemical senses	BS/FST/NEU/PHYS	England	1,099	31,394
Journal of medical virology	VIR	USA	901	29,250
Cell	BMB/CB	USA	714	29,085
Journal of virology	VIR	USA	822	28,746

GIM, Medicine, General, and Internal; ORL, Otorhinolaryngology; MS, multidisciplinary sciences; MRE, medicine, research, and experimental; BS, behavioral sciences; FST, food science and technology; NEU, neurosciences; PHYS, physiology; VIR, virology; BMB, biochemistry and molecular biology; CB, cell biology.

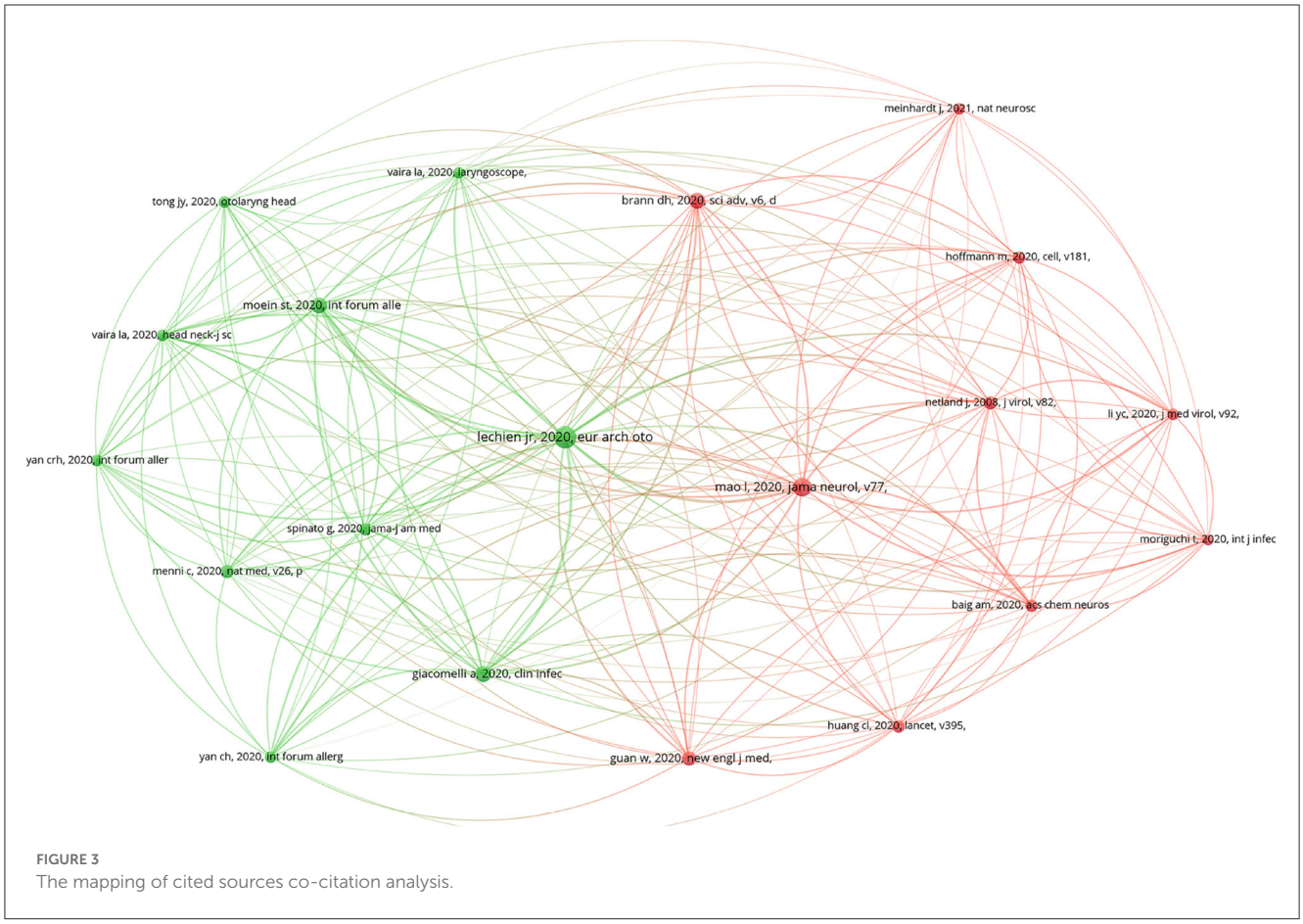

FIGURE 3
The mapping of cited sources co-citation analysis.

The LCS metric measures the number of citations between locally retrieved collections of literature, and can reflect the degree of attention given to specific literature within a particular field, similar to peer evaluation metrics. It can be seen from the results in Table 4 that the majority of the most influential literature in COVID-19 related OD research is concentrated in 2020 and 2021, with the exception of one research literature from 2008. The types of literature mainly involve Articles, Letters, Reviews, and Editorial Material. Both specialized literature with low GCS indicators and clinical research literature with high GCS indicators are represented.

These findings emphasize the significance of recent developments in the COVID-19 related OD research field, as

TABLE 4 Highly total link strength cited references (Top 20).

No.	Literature title	Type	Year	LCS	GCS	TLS
1	Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study (Lechien et al., 2020).	Article	2020	517	2,865	1,989
2	Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China (Mao et al., 2020).	Article	2020	358	6,641	1,529
3	Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study (Giacomelli et al., 2020).	Letter	2020	266	1,519	1,297
4	Smell dysfunction: a biomarker for COVID-19 (Moein et al., 2020).	Article	2020	256	781	1,217
5	Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia (Brann et al., 2020).	Article	2020	252	903	1,057
6	Severe acute respiratory syndromecoronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2 (Netland et al., 2008).	Article	2008	192	1,358	904
7	Alterations in smell or taste in mildly Symptomatic outpatients with SARS- CoV-2 infection (Spinato et al., 2020).	Letter	2020	167	732	806
8	Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases (Vaira et al., 2020a).	Article	2020	149	497	758
9	Clinical characteristics of coronavirus disease 2019 in China (Guan et al., 2020).	Article	2020	207	30,205	749
10	Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms (Baig et al., 2020).	Editorial Material	2020	154	2,395	746
11	Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms (Yan C. H. et al., 2020).	Article	2020	133	864	702
12	Self-reported olfactory loss associates with outpatient clinical course in COVID-19 (Yan C. R. H. et al., 2020).	Article	2020	134	348	692
13	The neuroinvasive potential of SARS- CoV2 may play a role in the respiratory failure of COVID-19 patients (Li et al., 2020).	Review	2020	146	2562	664
14	Real-time tracking of self-reported symptoms to predict potential COVID-19 (Menni et al., 2020).	Article	2020	177	1,236	640
15	SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor (Hoffmann et al., 2020).	Article	2020	167	17,297	635
16	Anosmia and ageusia: common findings in COVID-19 patients (Vaira et al., 2020b).	Article	2020	135	796	633
17	A first case of meningitis/encephalitis associated with SARS-Coronavirus-2 (Moriguchi et al., 2020).	Article	2020	128	2,164	618
18	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China (Huang et al., 2020).	Article	2020	160	50,435	532
19	The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta- analysis (Tong et al., 2020).	Review	2020	134	578	518
20	Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19 (Meinhardt et al., 2021).	Article	2021	131	979	342

well as the importance of considering both specialized and clinical research literature in evaluating the impact of this research area.

Figure 3 and Table 4 highlight the divided knowledge base of COVID-19 related OD research, with two main clusters identified based on the top 20 highly cited papers as determined by the VOSviewer LCS metrics. These clusters center around COVID-19 clinical research and specialized OD research topics.

The first cluster, which focuses on COVID-19 clinical research, is represented by the red area in Figure 3 and includes literature such as Netland et al. (2008), Baig et al. (2020), Brann et al. (2020), Guan et al. (2020), Hoffmann et al. (2020), Huang et al. (2020), Li et al. (2020), Mao et al. (2020), Moriguchi et al. (2020), and Meinhardt et al. (2021), among others. These articles delve into various aspects of COVID-19, including neurological symptoms, OD, the susceptibility of neurons to SARS-CoV-2, clinical features, and treatment options. In particular, Mao et al. (2020) conducted a case study on 214 COVID-19 patients in Wuhan, China and found a significant proportion of neurological symptoms, including central nervous system manifestations, peripheral nervous system manifestations, and skeletal muscle damage manifestations. Brann et al. (2020) explored the connection between SARS-CoV-2 infection of non-neuronal cells and OD in COVID-19 patients, while Netland et al. (2008) found that neurons were highly susceptible targets of SARS-CoV.

The second cluster of COVID-19 related OD research, as depicted by the green area in Figure 3, encompasses literature that focuses on specialized OD topics. This cluster comprises literature numbered 1, 3, 4, 7, 8, 11, 12, 14, 16, and 19 in Table 4. Literature No.1, with the highest LCS and TLS indicators among the specialized OD literature, is an investigation carried out by Lechien et al. (2020) who surveyed 417 patients with COVID-19 across 12 European hospitals. They found that olfactory and gustatory dysfunction were clinical manifestations of mild to moderate cases of COVID-19. In addition, literature numbered 3, 8, 11, and 19, as demonstrated by Giacomelli et al. (2020), Tong et al. (2020), Vaira et al. (2020a), and Yan C. H. et al. (2020), respectively, show that taste or smell impairment are symptoms commonly observed in SARS-CoV-2-positive hospitalized patients. Furthermore, literature numbered 4, 12, 14, and 16, as reported by Menni et al. (2020), Moein et al. (2020), Vaira et al. (2020b), and Yan C. R. H. et al. (2020), suggest that olfactory impairment is a feature of neoconiosis and that olfactory testing may be useful for identifying patients in need of early treatment or isolation. Lastly, Spinato et al. (2020) in literature No.7 assessed the prevalence, intensity, and duration of olfactory or taste alterations.

3.3. Emerging themes from the literature

In the present study, a keyword co-occurrence analysis was conducted on a corpus of 1,592 documents related to OD in the context of COVID-19. The VOSviewer tool was utilized to visualize the relationships between author keywords within this research area. The resulting graph presents author keywords as nodes, with larger nodes indicating a greater frequency of occurrence of these keywords. The line segments connecting these nodes represent the interrelatedness between the keywords, with thicker lines indicating a stronger association and shorter lines reflecting a closer connection.

Before conducting analysis in VOSviewer, a systematic data cleaning and term merging is carried out. For instance, in regards to keywords related to COVID-19, various terms such as "coronavirus disease 2019," "coronavirus disease 2019 (COVID-19)," "COVID-19," and "COVID-19" are standardized as "COVID-19." This process of term merging and data cleaning is crucial in maintaining consistency in terminology and enabling accurate analysis.

Subsequently, after carefully reviewing the dataset containing 2,649 author keywords, it was determined that those with a co-occurrence frequency exceeding 11 were deemed to be of particular significance. As a result, 62 keywords were selected and used to generate the keyword co-occurrence analysis graph depicted in Figure 4.

Figure 4 illustrates the results of the co-word analysis performed on the keywords utilized by authors in the field of COVID-19 and its related areas of study within the OD domain. The analysis reveals the existence of six clusters, each distinguished by a unique color, representing closely related hot topics. In order to succinctly convey the main concepts and hot topics of each cluster, Table 5 summarizes these findings.

The results of the high-frequency author keyword co-occurrence analysis, as depicted in Figure 4 and summarized in Table 5, demonstrate the major hotspots and emerging themes in COVID-19 related research within the OD domain. Utilizing the VOSviewer tool, the findings indicate that these themes can be broadly categorized into six clusters: COVID-19, long COVID, smell, anosmia, olfactory dysfunction, and recovery research. This information provides valuable insight into the current state and direction of COVID-19 related research.

Cluster 1 (Red): An examination of COVID-19 research was conducted and revealed the largest cluster, comprising 28 keywords. The most prevalent keyword, "COVID-19" (occurrences = 1,052, total link strength = 2,492), was found to be closely related to "SARS-CoV-2," "ACE2," "olfactory bulb," "CNS," "neurological manifestations," and other relevant terms.

Cluster 2 (Green): The second significant cluster was identified as related to the phenomenon of long COVID, which consisted of 12 keywords. The most frequently occurring keyword, "long COVID" (occurrences = 70, total link strength = 154), was found to be associated with "symptoms," "epidemiology," "children," "healthcare workers," "prevalence," and other related keywords.

Cluster 3 (Blue): This cluster, consisting of 10 keywords, was found to be related to the research area of smell. The most frequent keyword, "smell" (occurrences = 173, total link strength = 688), was shown to be one of many neurological symptoms affected by the "coronavirus" and "virus," impacting sensory perception and resulting in related neurological symptoms such as "olfaction," "taste," "gustatory," "hyposmia," "hypogeusia," and others.

Cluster 4 (Yellow): Our analysis revealed the emergence of a cluster centered around the theme of anosmia, with six keywords identified. The keyword "Anosmia" had the highest frequency of occurrence (occurrences = 370, total link strength = 1,259) and was found to be strongly associated with "dysgeusia," "ageusia," "taste loss," and "coronavirus infections," and "SARS-CoV-2 infection."

Cluster 5 (Purple): Another cluster was identified that pertains to OD, encompassing three keywords. The keyword "olfactory dysfunction" was the most frequently occurring among these keywords (occurrences = 255, total link strength = 788) and was observed to have a causal relationship with "olfactory training" and "quality of life."

Cluster 6 (Turquoise): The sixth cluster identified in our analysis pertained to the theme of Recovery, with three keywords

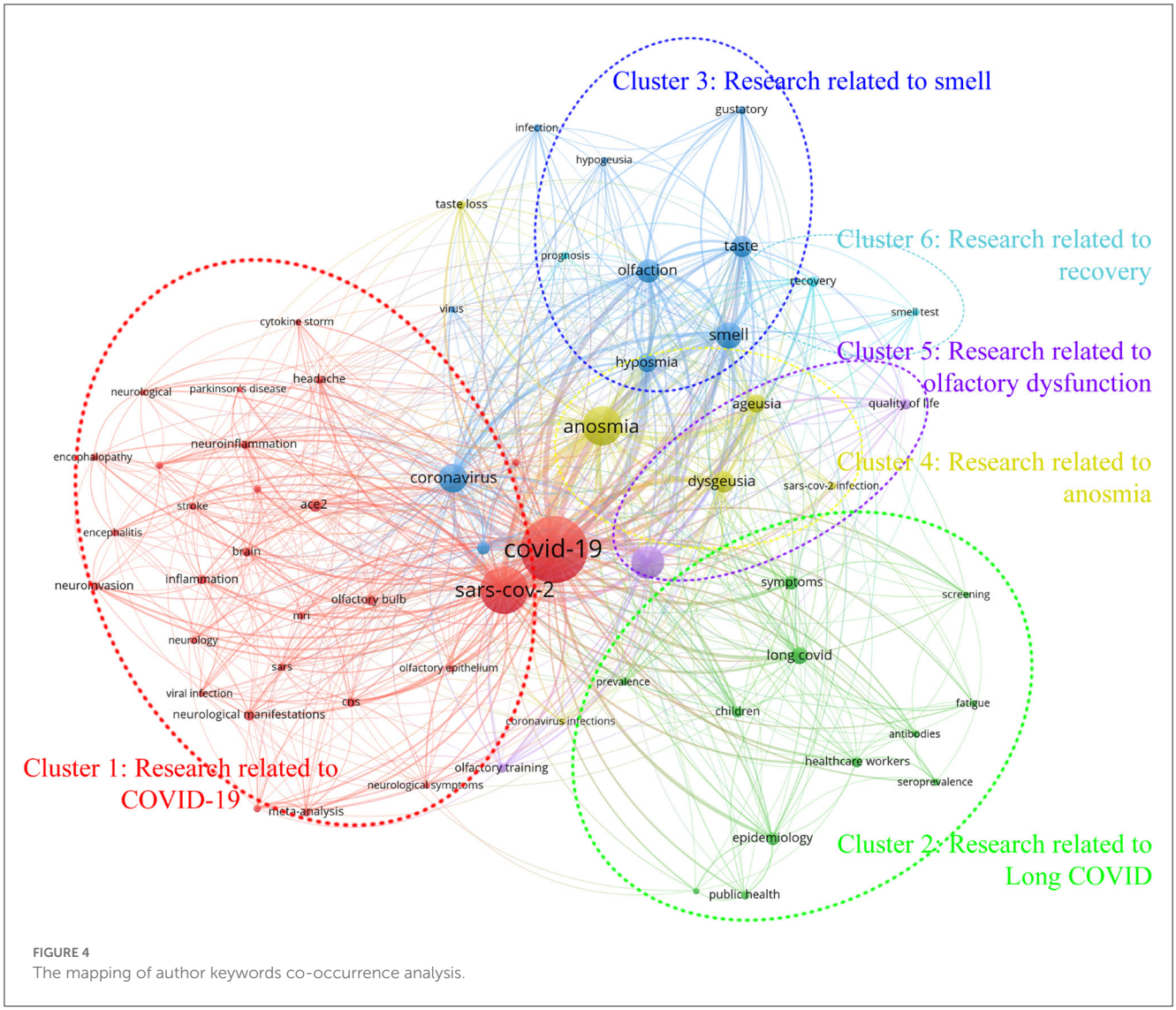

FIGURE 4
The mapping of author keywords co-occurrence analysis.

TABLE 5 Research concepts and hot topics.

Cluster	Concept	Nodes (n=62)
1	COVID-19	ACE2, brain, CNS, COVID-19, cytokine storm, encephalitis, headache, encephalopathy, viral infection, inflammation, meta-analysis, MRI, neurodegeneration, neuroinflammation, neuroinvasion, neurological, neurological manifestations, neurological symptoms, neurology, neurotropism, olfactory bulb, olfactory epithelium, Parkinson's disease, risk factors, SARS, SARS-CoV-2, stroke, systematic review (n = 28)
2	Long COVID	Antibodies, children, epidemiology, fatigue, healthcare workers, infectious disease, long COVID, prevalence, public health, screening, seroprevalence, symptoms (n = 12)
3	Smell	Coronavirus, gustatory, hypogeusia, hyposmia, infection, olfaction, pandemic, smell, taste, virus (n=10)
4	Anosmia	Ageusia, anosmia, coronavirus infections, dysgeusia, SARS-CoV-2 infection, taste loss (n = 6)
5	Olfactory dysfunction	Olfactory dysfunction, olfactory training, quality of life (n = 3)
6	Recovery	Prognosis, recovery, smell test (n = 3)

identified. The keyword "recovery" was the most frequently occurring among these keywords (occurrences = 29, total link strength = 113) and was observed to be associated with "smell test" and "prognosis."

The largest of the six study clusters discussed is COVID-19, where evidence has emerged that SARS-CoV-2 infecting Angiotensin-converting enzyme 2 (ACE2) leads to olfactory impairment in patients with neocoronary pneumonia (Bilinska

et al., 2020). The presence of the virus in the olfactory epithelium and bulb further highlights the critical role that olfaction plays in the potential pathways of SARS-CoV-2 entry into the central nervous system (CNS) (Lima et al., 2020; Klingenstein et al., 2021). The growing body of research supports the notion that SARS-CoV-2 can target the nervous system, leading to various neurological manifestations, including loss of smell and taste (Divani et al., 2020). The second largest cluster is "long COVID," which refers to symptoms, signs, and adverse reactions that persist for a prolonged period following neocoronavirus infection. Among the symptoms of Long COVID, Liao et al. (2022) have noted that olfactory and gustatory disturbances may be the primary symptoms in patients with long COVID-19. A significant proportion of patients reportedly develop persistent chemosensory impairments, including olfactory and taste disturbances, ranging from 3 months to 2 years after the onset of symptoms.

Studies from both the COVID-19 and long COVID clusters suggest that SARS-CoV-2 can result in neurological manifestations, including loss of smell, which may present as a persistent phenomenon in long COVID patients.

Within the six research clusters, four clusters, including smell, anosmia, olfactory dysfunction, and recovery, are focused on OD and its related themes. Multiple studies have reported that the senses of smell and taste are the most frequently impacted in patients with neocoronary pneumonia, with OD and taste impairment being key symptoms of the illness (Lechien et al., 2020; Yan C. H. et al., 2020; Ferrulli et al., 2022). Among them, OD is classified into two levels: olfactory loss (anosmia) and olfactory decline (hyposmia). The accurate detection, diagnosis, treatment, olfactory training, recovery, and prognosis of OD in neocoronary pneumonia patients are essential to enhance their quality of life.

4. Discussion

4.1. Research trend under the perspective of time

Given the rapidly evolving nature of COVID-19, with its alarming rate of transmission and the emergence of new mutant strains, it is imperative to have a comprehensive understanding of the spatiotemporal evolution of related research results. Therefore, in this paper, based on the clusters of Figure 4 and their keywords, and subsequently combined with the average year of publication values of each keyword counted in VOSviewer, we produced the mapping of keywords in six clusters of COVID-19 related OD temporal evolution, as shown in Figure 5, thus revealing the temporal trends of related studies.

As depicted in Figure 5, the temporal evolution of COVID-19 related OD research can be characterized by three distinct phases. The second phase, which began in the beginning of 2021, is the phase where the majority of the keywords in the six clusters of COVID-19 related OD research show a concentrated peak, particularly for keywords such as COVID-19, smell, anosmia, olfactory dysfunction, and recovery. This suggests that the world was facing its most challenging moment in terms of COVID-19 during this phase, with a significant shortage of medical resources in several countries and an immediate need for extensive COVID-19-related research efforts. The first phase encompasses the period prior to the start of 2021, during which the impact of COVID-19 on patients' sense of taste and smell was gradually being recognized. This phase saw the initial attention from researchers toward the topics of SARS, CNS, ACE2, and taste loss. Finally, the third phase, which began in 2021, has seen a consolidation of the objective fact that COVID-19 causes OD symptoms. This stage has witnessed a shift in research focus toward new areas, such as long COVID, olfactory bulb, fatigue, olfactory training, quality of life, among others.

4.2. Suggestions on future research

4.2.1. Understanding the mechanisms of OD

Several studies have explored the mechanisms underlying OD in COVID-19 patients. Pujadas et al. (2021) conducted a molecular profiling autopsy study and revealed the damage to the olfactory bulb caused by the New Coronary Pneumonia. Sharma et al. (2021) reviewed the entry pathways and pathogenic mechanisms of SARS-CoV-2 into the central nervous system, including the olfactory and retinal nervous systems. Najafloo et al. (2021) examined the mechanisms associated with olfactory impairment in neocoronary pneumonia, including olfactory cleft syndrome, local inflammation, apoptosis of olfactory cells, and damage to olfactory neurons and stem cells.

Sodagar et al. (2022) reviewed the pathological features, neuroinflammatory mechanisms, and potential treatments of SARS-CoV-2 in the brain, finding strong infection of the olfactory bulb, thalamus, and brainstem. Karimian et al. (2022) explored the molecular mechanism of SARS-CoV-2-induced olfactory deficit, suggesting that OD may be a temporary or long-term complication caused by olfactory neuroepithelial disorders, with the Delta and Omicron strains relying on TMPRSS2 to enter cells and inducing inflammation, apoptosis, and neuronal damage.

Despite these advances, there remains a significant knowledge gap regarding the possible mechanisms leading to olfactory loss (Dunai et al., 2022). Further studies are urgently needed to better understand and identify the causes of OD in COVID-19 patients, in order to improve prevention and treatment strategies (de Melo et al., 2021).

4.2.2. Assessment of OD

In recent years, various tools and methods have been employed to evaluate OD in patients with COVID-19. For instance, Duff et al. (2022) utilized brain magnetic resonance imaging (MRI) to assess the neuropsychiatric consequences of neocoronary pneumonia, demonstrating the high reliability of multiple imaging derived phenotypes (IDPs) in measuring the impact of SARS-CoV-2 infection on the brain through potential pathogenic mechanisms. Melkumyan et al. (2022) conducted a cross-sectional study that analyzed the sensitivity to olfaction and trigeminal nerve-triggered olfaction, as well as the ability to distinguish between different odors, in patients recovering from neocoronary pneumonia and revealed pathological changes in olfactory and

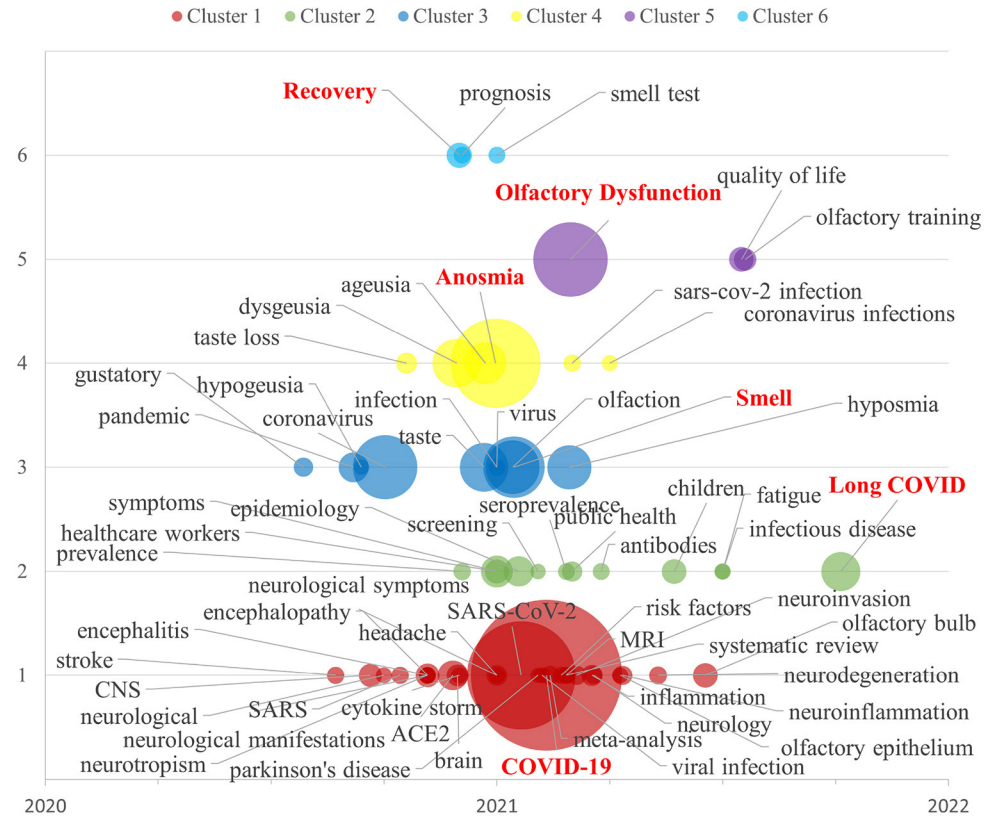

FIGURE 5
The mapping of keywords temporal evolution.

trigeminal perceptual abilities that result in OD. Kim and Min (2022) proposed a psychophysical assessment system for OD in neocoronary pneumonia patients using a universal odorant that is free from the risk of viral transmission, which may provide early diagnosis and management of such patients. Ciofalo et al. (2022) used the Visual Analogue Scale (VAS) to prospectively evaluate nasal and olfactory symptoms in 162 neocoronary pneumonia patients. Gupta et al. (2022) utilized the Novel Anosmia Screening at Leisure (NASAL) patient report to assess olfactory perception, demonstrating its efficacy in identifying OD in patients.

These studies suggest that the use of OD assessment tools or methods can aid in our understanding of the prevalence of the disease and facilitate the development of effective treatments. However, further research is necessary in this field, particularly to establish standardized assessments that can more accurately measure OD in patients with COVID-19.

4.2.3. Interventions of OD

In addressing OD in patients with neocoronary pneumonia, a range of therapeutic approaches have been evaluated, including oral supplementation, topical medications, nasal rinses, and olfactory training.

Hosseinpoor et al. (2022) and Vaira et al. (2022) studied the effect of intranasal corticosteroid treatment on long-term OD recovery caused by COVID-19. At the same time, Veronese et al. (2022) found that the combination of olfactory rehabilitation and oral supplementation of palmitoyl ethanolamine and lidocaine can improve the treatment effect of post-conjunctivitis OD. A review by Gao et al. (2022) reported that topical herbal therapies demonstrated positive effects in the treatment of OD. Additionally, a study by Forouzanfar et al. (2022) revealed that diets containing pomegranate juice and lacquer sap were effective in reducing symptoms such as olfactory and gustatory dysfunction in patients with neoconjunctivitis.

As for olfactory training, Hwang et al. (2023) evaluated the impact of olfactory training on OD in patients with neocoronary pneumonia. It is found that olfactory training was effective in improving OD caused by neocoronary pneumonia both in the acute and chronic phases. Khan et al. (2022) conducted a randomized clinical trial on the efficacy of combined visual-olfactory training in patients with olfactory loss due to neocoronary pneumonia. The results of the trial suggest that bimodal visual-olfactory training may benefit patients with neocoronary pneumonia, although the efficacy of fragrance treatment has not yet been established.

In conclusion, multiple drug and non drug interventions have shown good results in the OD treatment of patients with COVID-19. Further research is needed to determine the most effective treatment and explore the potential benefits of joint intervention. In addition, personalized intervention is needed for different groups (such as children, the elderly and patients with potential health

conditions) to better understand the impact of OD on these groups and develop personalized intervention measures.

4.2.4. Long COVID prognosis of OD

Several studies have investigated the prognosis of OD in patients with neocoronary pneumonia. Mendonca et al. (2022) reported that OD is more prevalent in patients with neocoronary pneumonia than in those with severe disease, and that the presence of olfactory hyposmia/anosmia may indicate a favorable prognosis in neocoronary pneumonia. Tan et al. (2022) found that a significant proportion of patients with neocoronary pneumonia may experience long-lasting changes in their sense of smell or taste, potentially exacerbating the impact of long COVID.

Ho et al. (2022) conducted autopsy assessments on patients with neocoronary pneumonia and found that the infection is associated with axonal damage and microangiopathy in the olfactory tissues, resulting in severe and permanent OD. A review by Ibrahim et al. (2022) explored the potential determinants of poor prognosis for neurological symptoms in neocoronary pneumonia and reported that the olfactory nerve is the most commonly affected cranial nerve, resulting in olfactory loss.

In conclusion, the long-term prognosis of OD in patients with neocoronary pneumonia is still hard to predict. Further studies are needed to ensure its recovery rate and persistence. This will be important in providing guidance and developing treatments for patients with persistent psychosis.

5. Conclusion

The COVID-19 pandemic has been a catastrophic public health event, with infection contributing to a significant increase in the global prevalence of OD symptoms, affecting the quality of life of long-term COVID-19 patients and posing a major challenge to human health. To address this challenge, it is crucial to raise awareness and further explore the underlying mechanisms of OD through research. Our study analyzed 1,592 publications related to COVID-19 related OD in the Web of Science database, demonstrating the broad interest of researchers from different disciplines and countries. The most influential findings in the field were published in otorhinolaryngology, medicine, general and internal medicine, virology, and neuroscience journals. The study identified six research hotspots, including COVID-19, long COVID, smell, anosmia, recovery, and olfactory dysfunction. These findings provide valuable insight into the temporal trends in COVID-19 related OD research and will aid future researchers in understanding and developing effective assessments, interventions, and prognostic options. Ultimately, a better understanding of the underlying mechanisms of OD in COVID-19 patients will be crucial in addressing the lasting legacy of the pandemic on human health.

Author contributions

YM and WB contributed to the writing and conception of the professional part of the study. ZY and JT contributed to the implementation of bibliometric methods and mapping. YM, ZY, and JT drafted the manuscript and performed the data analysis. WB and JT revised the manuscript and made critical suggestions on this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impairment of quality of life due to COVID-19-induced long-term olfactory dysfunction

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Introduction: Olfactory dysfunction is one of many long-lasting symptoms associated with COVID-19, estimated to affect approximately 60% of individuals and often lasting several months after infection. The associated daily life problems can cause a decreased quality of life.

Methods: Here, we assessed the association between perceived quality of life and both qualitative and quantitative olfactory function (distorted and weakened sense of smell, respectively) in 58 individuals who had undergone confirmed SARS-CoV-2 infection and who complained about olfactory dysfunction.

Results: Participants with large quantitative olfactory dysfunction experienced a greater reduction in their quality of life. Moreover, our participants had a high prevalence of qualitative olfactory dysfunction (81%) with a significant correlation between qualitative olfactory dysfunction and daily life impairment. Strong drivers of low quality of life assessments were lack of enjoyment of food as well as worries related to coping with long-term dysfunctions.

Discussion: These results stress the clinical importance of assessing qualitative olfactory dysfunction and the need to develop relevant interventions. Given the poor self-rated quality of life observed, healthcare systems should consider developing support structures, dietary advice, and guidelines adapted to individuals experiencing qualitative olfactory dysfunction.

KEYWORDS

olfactory disorders, parosmia, phantosmia, quality of life, COVID-19

Introduction

The COVID-19 pandemic has raised public awareness of olfaction and its importance for our health, wellbeing, and quality of life (Elkholi et al., 2021). One common acute symptom related to COVID-19 is olfactory dysfunction (Lechien et al., 2020), estimated to affect up to 70% of individuals with mild to moderate symptoms (Vaira et al., 2020). Many recover after a few days, but recent follow-up studies show that some patients still experience olfactory dysfunction 2 years after infection (McWilliams et al., 2022).

The mechanisms behind the pathophysiology of long-lasting olfactory dysfunction related to COVID-19 is still not known. However, reports of specific brain changes following infection have been observed. For example, COVID-19 patients with olfactory dysfunction display reductions in functional connectivity between the orbitofrontal cortex and dorsal anterior cingulate cortex

(Wingrove et al., 2023) as well as decreased gray matter volume surrounding olfactory-related regions such as the orbitofrontal cortex and parahippocampal gyrus (e.g., Douaud et al., 2022; Campabadal et al., 2023). These patients also show reduced blood flow in the orbital and medial frontal regions (Yus et al., 2022). In line with the notion that central dysfunction is the cause of long-term olfactory loss is data showing that when comparing pre- and post COVID-19 changes, the olfactory bulb volume is reduced in nearly all cases (Thunell et al., 2022).

Although central causes are reported in the literature, multiple causes linked to abnormalities in the peripheral system have also been reported (e.g., Finlay et al., 2022; Zazhytska et al., 2022) and it is likely that both peripheral and central mechanisms are at play.

The sense of smell provides important information about our environment and guides attention via perceived valence of odor sources, which allows us to avoid threats and approach rewards (Croy et al., 2014). For instance, olfaction plays a crucial role in assessing the edibility of an item (Stevenson, 2010) and is also protective by alerting to hazards, such as fire or gas (Pence et al., 2014). Olfactory dysfunction therefore incurs an increased risk of exposure to environmental hazards as well as food poisoning (Pence et al., 2014). Moreover, olfactory dysfunction is linked to impairments in both daily functioning and interpersonal relationships (Erskine and Philpott, 2020), which may negatively affect both physical and psychological health (Elkholi et al., 2021). Accordingly, people with long-term smell loss often exhibit depressive symptoms, diminished self-esteem, loss of intensity of emotional experiences (Schäfer et al., 2021), and lower overall quality of life (Miwa et al., 2001; Croy et al., 2014).

Most studies on olfactory problems focus on quantitative dysfunction, i.e., hyposmia (decreased sensitivity) and anosmia, so-called "smell blindness." However, COVID-19 has been reported to also cause qualitative olfactory dysfunction, i.e., parosmia (distorted smells) and phantosmia (odor hallucinations) in around 40–50% of individuals who experience decreased sensitivity during or after the infection (Hopkins et al., 2021; Frasnelli et al., 2022). Qualitative olfactory impairments often onset months after infection, may last for a long time (Gary et al., 2022), and have been reported to have a stronger negative impact on the quality of the individual's life than quantitative dysfunctions alone (Leopold, 2002; Frasnelli and Hummel, 2005). Indeed, COVID-19 patients with parosmia show reduced quality of life and rate their situation as worse than do those without parosmia (Otte et al., 2022).

COVID-19-related reductions in quality of life are well described in the literature, as are the negative effects of an impaired sense of smell on quality of life, but it is still unclear which specific aspects of COVID-19 related olfactory dysfunction are related to prolonged decreased quality of life. Here, we assessed qualitative and quantitative olfactory dysfunction in individuals who had previously undergone SARS-CoV-2 infection and hypothesized a positive correlation between the former and daily life impairment. Identifying the causes of decreased quality of life will aid risk prediction and facilitate the development of interventions.

Methods

Participants

Participants (n =138) were recruited from the longitudinal COMMUNITY (COVID-19 Immunity) Study, in which all participants continuously have been tested for seroprevalence of SARS-CoV-2 antibodies since the beginning of the pandemic (Rudberg et al., 2020). Two of these were excluded due to problematic testing conditions and one due to being diagnosed with a disorder known to change the sense of smell. None of the individuals suffered from nasal congestion or rhinorrhoea, conditions associated with olfactory dysfunction (Landis et al., 2003; Doty and Kamath, 2014). Another 40 participants had never tested positive for SARS-CoV-2 antibodies and were therefore excluded. From the remaining 95 participants who had at some point tested positive for SARS-CoV-2 antibodies, only participants who experienced smell/taste-related problems (58) were instructed to fill out the form related to daily life impairment (QOD-NS; Table 1). The final dataset used in this study thus consists of 58 individuals. Detailed information related to the time since onset of COVID-19 was missing for 8 out of these participants. The study was approved by the Swedish Ethical Review Authority (Dnr: 2021-02052) and all participants provided written informed consent prior to participation. All procedures were in accordance with the Helsinki declaration. See Table 1 for details related to the participants.

Measurement

Qualitative olfactory dysfunction

To identify participants with qualitative olfactory dysfunctions, we used a questionnaire containing two dichotomous questions; (1) "Do you experience olfactory distortions, i.e., that smells have changed after COVID" and (2) "Do you experience phantosmia after COVID (olfactory hallucinations/phantom smells)?" An affirmative answer to question 1 categorized the participants as parosmic and an affirmative answer to question 2 categorized them as phantosmic. The participants additionally answered four structured questions about their experienced degree of qualitative olfactory dysfunction (Landis et al., 2010) each with four response alternatives; this is never the case (assigned 1 point); this is rarely the case (2 points), this is often the case (3 points), this is always the case (4 points), yielding a minimum qualitative olfactory dysfunction score of 4 and a maximum of 16. Note that this scale is reversed as compared to Landis et al. (2010).

Quantitative olfactory dysfunction

We assessed quantitative olfactory ability using the Sniffin' Sticks extended test battery (Burghart Messtechnik, Holm, Germany), a validated psychophysical measure of olfactory ability (Hummel et al., 1997; Kobal et al., 2000; Sorokowska et al., 2015) commonly used to quantify olfactory deficits in COVID-19 patients (e.g., Iannuzzi et al., 2021; Prem et al., 2021; Stankevice et al., 2023). The test consists of a nasal chemosensory performance assessment utilizing felt tip pen-like devices for odor presentation and includes three subtests measuring odor threshold (T), odor discrimination (D), and odor identification (I); yielding a summarized (TDI) score of olfactory function where higher scores indicate better function. In the present study, the session begun with an odor threshold subtest using 16 triplets of pens where one pen in each triplet contained n-butanol and two were odorless. The task of the participant was to identify the pen with the odor when an experimenter presented consecutive triplets in a staircase procedure. The second subtest was focused on odor discrimination and contained 16 triplets of pens with various odorants. Two pens in each triplet contained the same odorant and the participant was instructed to select the pen that smelled different. The final subtest, an odor identification

TABLE 1 Descriptive statistics of research participants.

	Both (*N* =19)	Qualitative (*N* =28)	Quantitative (*N* =4)	None (*N* =7)	Total (*N* =58)
Sex					
Female	16 (84.2%)	24 (85.7%)	4 (100%)	6 (85.7%)	50 (86.2%)
Male	3 (15.8%)	4 (14.3%)	0 (0%)	1 (14.3%)	8 (13.8%)
Age (years)					
Mean (SD)	48.5 (11.7)	47.8 (11.2)	54.0 (11.0)	46.4 (11.0)	48.3 (11.2)
Time since COVID-19 (days)					
Mean (SD)	458 (30.1)	441 (68.3)	448 (45.3)	501 (34.0)	456 (54.6)

The group label Both indicates participants who were classified with both qualitative and quantitative olfactory dysfunction, and the group label None indicates participants who were classified with neither. The label Qualitative indicates participants with only qualitative dysfunction, and the label Quantitative indicates participants with only quantitative dysfunction.

TABLE 2 Daily life impairment (QOD-NS), quantitative (TDI) and qualitative (olfactory dysfunction score) olfactory measures grouped by olfactory dysfunction.

	Both (*N* =19)	Qualitative (*N* =28)	Quantitative (*N* =4)	None (*N* =7)	Total (*N* =58)
QOD-NS					
Mean (SD)	16.8 (9.97)	11.0 (7.95)	4.50 (5.26)	6.57 (4.24)	11.9 (8.97)
TDI					
Mean (SD)	23.1 (5.99)	33.9 (2.37)	28.8 (1.02)	33.9 (3.21)	30.0 (6.36)
Qualitative olfactory dysfunction score					
Mean (SD)	9.42 (2.32)	8.36 (2.50)	4.25 (0.500)	5.43 (1.27)	8.07 (2.71)

The group label Both indicates participants who were classified with both qualitative and quantitative olfactory dysfunction, and the group label None indicates participants who were classified with neither. The label Qualitative indicates participants with only qualitative dysfunction, and the label Quantitative indicates participants with only quantitative dysfunction.

task, included 16 pens with everyday odors. Participants were instructed to identify the odors using a multiple-choice answering format with a four-alternative card for each odor. All three subtests employed a forced-choice answering format. Based on normative data (Oleszkiewicz et al., 2019), anosmia was defined as a TDI score of ≤16, normosmia as a score of ≥30.75, and hyposmia as a score between these two values. Total testing time for each subject was approximately 1 h.

Daily life impairment

Self-assessment of daily life impairment related to olfactory dysfunction was performed using a Swedish translation of the shorter modified (Simopoulos et al., 2012) Questionnaire of Olfactory Disorders – Negative Statements subscale (QOD-NS) (Frasnelli and Hummel, 2005), a widely used questionnaire evaluating the negative impact of smell loss on quality of life. The measure is a four-scale questionnaire targeting the degree of experienced suffering related to olfactory dysfunction by utilizing a Likert-scale based on 17 items where participants could either agree (3 points), partly agree (2 points), partly disagree (1 point), or disagree (0 points) with various statements. The final score varies from a minimum of 0 and a maximum of 51, with higher scores indicating more severe daily life impairment.

Statistical analyses

All data and analyses included in this manuscript can be accessed from the Open Science Framework (OSF) at https://osf.io/czeq3/?view_only=8ad63cac2cd94121b954f47a403fab0e. Statistical analyses were performed using the statistical software R (v4.2.2; R Core Team, 2022) and the packages cocor (v1.1.4; Diedenhofen and Musch, 2015), dplyr (v1.0.10; Wickham et al., 2022a), ggplot2 (v3.4.0; Wickham, 2016), ggridges (v0.5.4; Wilke, 2022), haven (v2.5.1; Wickham et al., 2022b), likert (v1.3.5; Bryer and Speerschneider, 2016), psych (v2.2.9; Revelle, 2022), table1 (v1.4.2; Rich, 2021), and tidyr (v1.2.1; Wickham and Girlich, 2022). Calculation for the test of the difference between two dependent correlations with one variable in common was carried out using quantpsy.org computer software (Lee and Preacher, 2013). The significance criterion for all statistical tests was set to $\alpha = 0.05$.

Results

Qualitative olfactory dysfunction

We first set out to determine the prevalence of qualitative olfactory dysfunction (parosmia; distorted odor perception and phantosmia; phantom smells) in our sample based on participants' subjective answers to the questionnaire. Forty-seven out of 58 individuals (81%) experienced qualitative problems, out of which 21 individuals reported both parosmia and phantosmia, 25 only parosmia, and one only phantosmia. Further, there was a large co-occurrence of quantitative and qualitative olfactory dysfunction (Table 2). Seven of the participants included in this analysis were classified as having neither quantitative nor qualitative dysfunction, despite reporting that they experienced problems.

Quantitative olfactory dysfunction

Next, we assessed quantitative olfactory dysfunction, as defined by the TDI scores. Twenty-three (40%) of our participants scored in accordance with quantitative olfactory dysfunction; 20 were classified as hyposmic (weakened sense of smell) and 3 were classified as anosmic (unable to use their sense of smell). Overall, TDI scores ranged from 12 to 40. See Table 2 for details.

Daily life impairment

Last, we computed quality of life impairment scores based on the QOD-NS questionnaires to assess how it is influenced by the qualitative and quantitative olfactory impairments (Table 2). As can be seen in Figure 1, the distributions of QOD-NS scores differed between clinical groups with a wider tail distribution and more extreme values for participants with qualitative and those with both qualitative and quantitative problems as compared with participants with quantitative or no impairment.

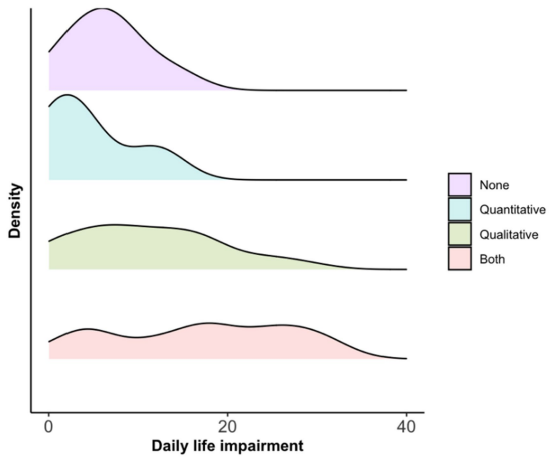

FIGURE 1
Density of distribution of average daily life impairment (QOD-NS score) assessments per olfactory dysfunction group.

Next, we wanted to know whether there was a link between degree of impairment and the individuals' rated quality of life. Using Spearman's rank correlation, we found that daily life impairment was positively correlated with the degree of qualitative olfactory dysfunction ($r = 0.57$, $p < 0.001$; Figure 2A). Similarly, a correlation was found between daily life impairment and quantitative olfactory function ($r = -0.38$, $p < 0.005$; Figure 2B).

To compare if daily life impairment had a significantly larger association with qualitative than quantitative olfactory dysfunction, we carried out a Fisher's r-to-z transformation followed by Steiger's (1980) equations to compute asymptotic covariance of the estimates. The difference between the correlation coefficients linking daily life impairment to qualitative and quantitative dysfunction, respectively, was not significant ($z = 1.41$, $p = 0.16$). In our sample, the qualitative olfactory dysfunction and quantitative olfactory function were correlated ($r = -0.26$, $p < 0.05$; Figure 3), meaning that there was some degree of comorbidity which might make separate assessments problematic.

To better understand what aspects of daily life were impaired, we also looked for trends in the answers to the specific questions of the QOD-NS. We found that negative experiences related to eating seemed like the most prevalent theme, whereas problems concerning relationships or changes in social behavior were rare (Figure 4).

Discussion

Here we show that 80% of individuals with lingering olfactory dysfunction from a COVID-19 infection still experience associated

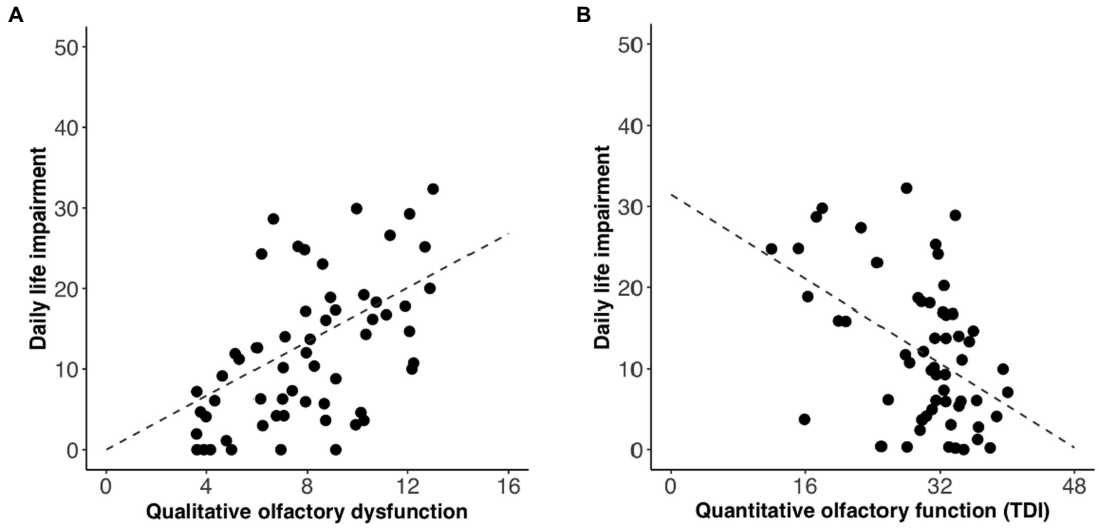

FIGURE 2
Relationship between average daily life impairment (QOD-NS score) and **(A)** degree of qualitative olfactory dysfunction and **(B)** quantitative olfactory function. Each data point represents one participant. Regression line is indicated by the intersected line. Scores are slightly jittered for visibility.

impairments in their quality of life more than a year after infection. To a great extent, this is due to their qualitative olfactory dysfunction. Qualitative olfactory dysfunction can be a debilitating condition, previously shown to correlate with higher rates of anxiety and depression (Philpott and Boak, 2014). In our sample, qualitative olfactory dysfunction was twice as common as quantitative dysfunction, and only four participants suffered from quantitative olfactory dysfunction without experiencing also qualitative olfactory dysfunction. Our data confirm that the severity of this prevalent qualitative olfactory dysfunction is positively correlated with daily life impairment. This is explained by specific themes related to daily life impairment, where daily life seems to be most negatively impacted by a change in eating patterns; potentially because social situations involving eating tend to be more affected by qualitative changes in smell than quantitative problems. For example, many individuals with parosmia are unable to ingest certain food items because they are disgusted by the smell, whereas hyposmia will not elicit the same strong affective reaction. Although daily life impairment seemed more strongly associated with qualitative dysfunction than quantitative dysfunction, no significant difference was found between the correlations. Therefore, we cannot conclude that daily life impairment is associated with qualitative dysfunction to a greater extent than with quantitative dysfunction. However, it is worth noting that there was a considerable comorbidity between the two diagnoses meaning that a firm separation is difficult to achieve.

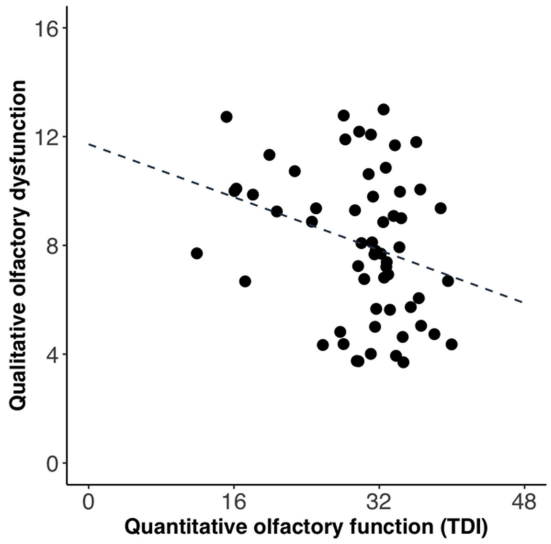

FIGURE 3
Relationship between qualitative olfactory dysfunction and quantitative olfactory function. Each data point represents one participant. Regression line is indicated by the intersected line. Scores are slightly jittered for visibility.

Considerable similarities between COVID-19-associated olfactory dysfunction and other types of post-viral olfactory dysfunction have previously been established via meta-analysis (Imam et al., 2020). There is therefore no reason to believe that our results are limited to COVID-19-related olfactory dysfunction, but rather they likely apply also to smell-related problems caused by other viral infections. However, olfactory dysfunctions due to other reasons such as head trauma or neurodegenerative disorders may yield other results. In our sample, it appears that those with no olfactory dysfunction reported higher average daily life impairment scores than the group with quantitative dysfunction. One reason why these normosmic individuals experienced a decreased quality of life may be that they noticed a decrease in olfactory function compared to their pre-COVID-19 olfactory function. However, firm conclusions based on this small sample size should be avoided.

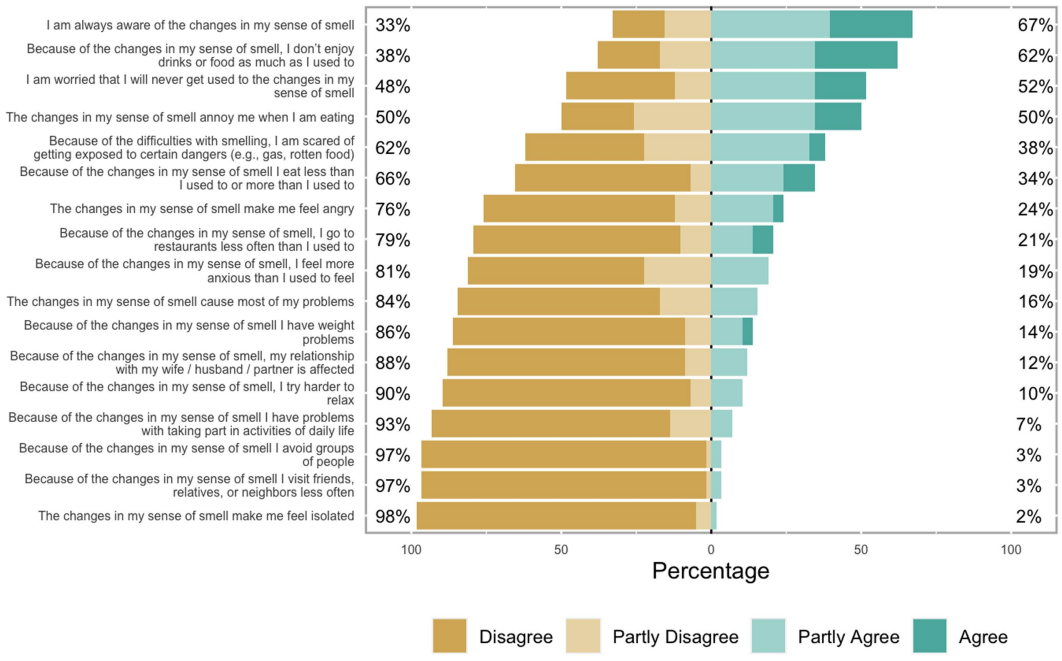

FIGURE 4
Response frequency to the questions of QOD-NS.

A recent meta-analysis suggested that women are less likely than men to regain their sense of smell (Tan et al., 2022), which might partially explain the large proportion of women signing up for the current study. However, the uneven sex distribution might also simply be due to the skewed sex balance of the population of healthcare workers from which the sample was taken. The strength of this study is the extensive psychophysical testing done in a homogenous group that was continuously monitored for COVID-19 infection from the onset of the pandemic. As mentioned previously, disruptions of daily life related to qualitative olfactory dysfunction may cause mental health related problems (e.g., Miwa et al., 2001; Croy et al., 2014; Elkholi et al., 2021; Schäfer et al., 2021). Recent data show that individuals experiencing olfactory dysfunction also report a lack of support from the medical field (Ball et al., 2021; Kye Wen Tan et al., 2022), providing incentive to further investigate the condition and develop evidence-based treatment specifically targeting qualitative olfactory dysfunction. Moreover, the present study did not exclude, nor control for, participants with long-covid syndrome or other related symptoms. Recent studies have shown associations between olfactory-related quality of life and affective as well as cognitive dysfunctions. For example, COVID-19 related olfactory dysfunction has been related to mood disturbances (Llana et al., 2023), a higher likelihood of depression (Liu et al., 2022), as well as cognitive dysfunction (Delgado-Alonso et al., 2022). The observed relationship between olfactory dysfunction and quality of life could therefore be mediated by other affective or cognitive symptoms. Hopefully, future studies will be able to replicate this type of extensive testing on highly controlled groups in a larger sample.

In conclusion, COVID-19 can cause long-lasting problems, and a large number of recovering individuals still experience olfactory dysfunction more than a year after infection. We found that individuals who suffer from lingering qualitative olfactory dysfunction experience limitations in daily life, in particular related to food and eating. Because qualitative olfactory dysfunction is known to be associated also with depression and anxiety, our results further stress the clinical importance of acknowledging it for risk predictions in future clinical research; as well as in the development of new interventions, such as support structures, dietary advice, and guidelines.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/czeq3/?view_only=8ad63cac2cd94121b954f47a403fab0e.

Ethics statement

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority (Dnr: 2021-02052). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JL contributed to conception and design of the study. AW collected the data, performed the statistical analysis, and wrote the first draft of the manuscript. ET, JL, and SH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Persistent olfactory dysfunction associated with poor sleep quality and anxiety in patients with long COVID

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Introduction: Poor sleep quality have been widely reported in patients with long COVID. Determining the characteristics, type, severity, and relationship of long COVID with other neurological symptoms is essential for the prognosis and management of poor sleep quality.

Methods: This cross-sectional study was conducted at a public university in the eastern Amazon region of Brazil between November 2020 and October 2022. The study involved 288 patients with long COVID with self-report neurological symptoms. One hundred thirty-one patients were evaluated by using standardised protocols: Pittsburgh sleep quality index (PSQI), Beck Anxiety Inventory, Chemosensory Clinical Research Center (CCRC), and Montreal Cognitive Assessment (MoCA). This study aimed to describe the sociodemographic and clinical characteristics of patients with long COVID with poor sleep quality and their relationship with other neurological symptoms (anxiety, cognitive impairment, and olfactory disorder).

Results: Patients with poor sleep quality were mainly women (76.3%), 44.04±12.73 years old, with >12 years of education (93.1%), and had monthly incomes of up to US $240.00 (54.2%). Anxiety and olfactory disorder were more common in patients with poor sleep quality.

Discussion: Multivariate analysis shows that the prevalence of poor sleep quality was higher in patients with anxiety, and olfactory disorder is associated with poor sleep quality. In this cohort of patients with long COVID, the prevalence of poor sleep quality was highest in the group tested by PSQI and were associated with other neurological symptoms, such as anxiety and olfactory dysfunction. A previous study indicates a significant association between poor sleep quality and psychological disorders over time. Recent studies involving neuroimaging found functional and structural changes in Long COVID patients with persistent

olfactory disfunction. Poor sleep quality are integral part of complex changes related to Long COVID and should be part of patient's clinical management.

KEYWORDS

long COVID, neurological manifestations, sleep disorders, olfaction disorders, anxiety

Introduction

Long COVID is a multisystem condition characterized by presence of signs and symptoms during or after COVID-19 that persisted for more than 4 weeks and which cannot be explained by an alternative diagnosis (Raveendran, 2021; Davis et al., 2023). Most patients diagnosed with long COVID were female (59.8%), was aged 36 to 50 (34.6%) and had not been hospitalized (75.8) (FAIR, 2022).

Hundreds of biomedical findings have been documented, with many patients experiencing dozens of symptoms across multiple system (Davis et al., 2021; Lopez-Leon et al., 2021). In the neurological system, neuropsychiatric disorders such as depression, anxiety, post-traumatic stress disorders (PTSD), and sleep disturbance being the most prevalent (Bacaro et al., 2020; Jinglong et al., 2020; Akinci and Basar, 2021). Poor sleep quality have been widely reported as a result of the restrictions imposed during the initial phase of the pandemic (Altena et al., 2020; Blume et al., 2020; Alrasheed et al., 2021) and as a symptoms in the acute phase of the disease (Felician et al., 2022; Smith et al., 2022) and after recovery (Cénat et al., 2021; Beck et al., 2021). Several ongoing studies focus on the duration of these disorders (transient/persistent).

Sleep plays a vital role in maintaining mental and physical health; a single night of sleep deprivation can weaken the immune system and trigger other disorders (Ibarra-Coronado et al., 2015; Innocenti et al., 2020; El Sayed et al., 2021). Sleep quality is essential for memory consolidation, including sensory memory like taste and smell (Velluti, 1997; Barnes and Wilson, 2014). Determining the characteristics, type, severity, and relationships of long COVID with other symptoms is essential for the prognosis and management of poor sleep quality. This study describes the sociodemographic and clinical characteristics of patients with long COVID with persistent poor sleep quality following severe acute COVID-19 and their relationship with other symptoms (anxiety, cognitive impairment, and olfactory disorder).

Materials and methods

Ethical aspects

This study was conducted in accordance with ethical standards and the Helsinki declaration and its later amendments. The ethics and research committee of the State University of Pará (Belem, Brazil) approved this study (Opinion No. 4,252,664), and written informed consent was obtained from all participants included in the study.

Study population and site

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (Cuschieri, 2019) and was conducted on patients who were enrolled for a follow-up programme for long COVID at a public university in the eastern Amazon region, Brazil. The study participants included men and women ≥18 years old with long-term neurological complaints who underwent reverse transcriptase-polymerase chain reaction or serological testing.

Three hundred nineteen patients were contacted and evaluated medically (anamnesis and neurological tests) between November 2020 and October 2022. Of the 319 patients, 31 were excluded due to previous neurological sequelae. The remaining 288 patients were evaluated using the following diagnostic instruments: Beck Anxiety Inventory for diagnosis of anxiety disturbances, Chemosensory Clinical Research Center (CCRC) for olfactory evaluation, and Montreal Cognitive Assessment (MoCA) for cognitive evaluation. Furthermore, 131 patients with complaints of sleep quality following severe acute COVID-19 were evaluated using the Pittsburgh sleep quality index (PSQI) for sleep quality evaluation. The PSQI evaluation results and this group's clinical data were compared to 157 patients without sleep complaints (Figure 1).

Study design, data collection, and procedures

This is an observational, cross-sectional study. A standardised evaluation form was used to collect sociodemographic and clinical data. The form contains data on education, sex, monthly income, and all symptoms associated with long-term COVID (such as headache, ageusia, fatigue, dyspnoea, myalgia, chest pain, back pain) and poor sleep quality that started after COVID-19 infection that could not be explained by other factors. Patients with suspected long-term COVID-related fatigue were evaluated by a multidisciplinary team and a neurologist regarding the nature of the symptoms, the time of onset and their impact on functional status. Aspects of premorbid and intercurrent mental health, mainly in relation to symptoms of depression, anxiety and post-traumatic stress disorder were also collected during the clinical interview. A short physical examination was conducted to assess pulmonary and cardiac functions and neurological findings.

The monthly income assessment was included in our initial interview as part of the socio-demographic data, the objective was to collect data that help answer possible iterations between the socioeconomic level and the development of long COVID. Such data is especially important in treatment of patients from the public health system in Brazil. The period for the calculation was the month referring to the date of the interview, first categorized into ranges based on the current minimum wage in Brazil and subsequently converted into US dollars.

The PSQI was used to evaluate sleep quality. The use of the PSQI followed the original recommendations (Buysse et al., 1998) in the Brazilian version (Bertolazi et al., 2011) with regard to sleep quality from

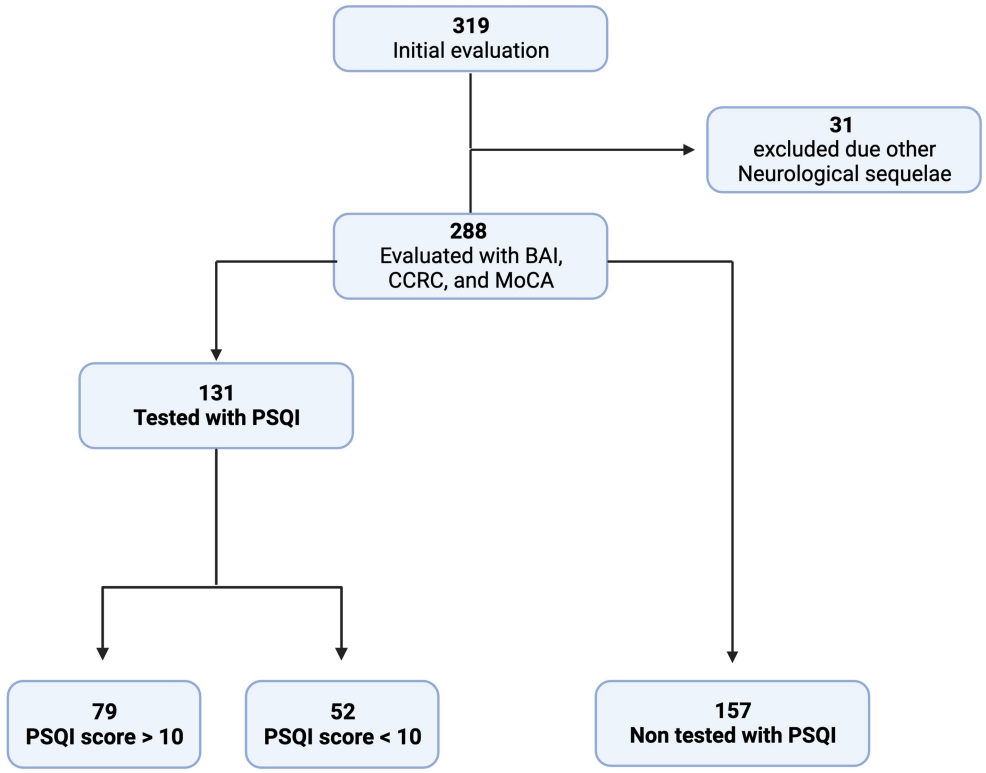

FIGURE 1
Flowchart of the study. BAI: Beck Anxiety Inventory. CCRC: Connecticut Chemosensory Research Center. MoCA: Montreal Cognitive Assessment. PSQI: Pittsburgh Sleep Quality Index.

the preceding month. Each patient answered 19 questions separated into seven components that included sleep quality, sleep latency, sleep duration, habitual sleep efficiency, poor sleep quality, sleeping medication, and daytime dysfunction. Each component had scores ranging from 0–3, with a total score of 21 points. Sleep quality staging followed the following classification: A PSQI score < 5 indicate a good sleep quality, and a PSQI score > 5 indicate a poor sleep quality. Patients with a PSQI global score > 5 indicates that the individual is having severe difficulties in at least two areas, or moderate difficulties in more than three areas. The global score is therefore "transparent," i.e., it conveys information about the severity of the individual's problem, and the number of problems present, through a single simple measure (Buysse et al., 1998).

Patients were grouped in two groups: individuals non-tested by PSQI and individuals tested by PSQI that clinical characteristics were compared. The individuals tested by PSQI was subdivided in PSQI score ≤ 10, and PSQI > 10, that were compared. Univariate and multivariate logistic regression analyses were performed to define the associated odds ratio between the poor sleep quality, epidemiological and clinical characteristics of the sample: sex, hospitalization, duration of long COVID symptoms, anxiety, mild cognitive impairment, olfactory disorder, ageusia, fatigue, and dyspnoea.

Statistical analysis

The collected data were tabulated in a Microsoft Excel™ spreadsheet (Microsoft Inc., Richmond, WA, United States). The GraphPad Prism software version 6.0.1™ (GraphPad, San Diego, CA, United States) was used for statistical analysis. D'Agostino–Pearson test was used to determine the normality of samples. Continuous variables data were presented as mean ± standard deviation and categorical variables were presented as absolute and relative frequencies. Student *t*-test was used to access parametric data. Non-parametric data were assessed using the Wilcoxon test. The categorical variables were assessed by the chi-square test or Fisher's exact test, as appropriate. A Binary logistic regression analysis was performed. The association between the patient's exposure factors (female sex, hospitalization, time from symptoms onset, fatigue, dyspnoea, anxiety, olfactory disorder, ageusia, mild cognitive impairment) and the outcome (poor sleep quality) was tested, with the calculation of raw odds ratios (OR) for each exposure factor, and respective confidence intervals (CIs). The arrangement with a better calculated r^2 was considered. An alpha level of 5% ($p < 0.05$) was adopted to reject the null hypothesis.

Results

The patients tested by PSQI were mainly women $n = 100$ (76.3%), 44.04 ± 12.73 years old (mean ± standard deviation), with >12 years of education $n = 122$ (93.1%), and had monthly incomes of up to US $240.00 (54.2%). Only 17 (12.9%) patients were admitted to the hospital during their acute phases of COVID. Their mean duration of symptoms was 265.66 ± 144.42 days, which was not statistically different from the group with no sleep complaints. Anxiety [non-tested

TABLE 1 Sociodemographic and clinical characteristics of patients evaluated by groups (n=288).

Variable	General (n =288)	Non-tested by PSQI (n =157)	Tested by PSQI (n =131)	p-value
Sex				
Female, n (%)	218 (75.7)	118 (75.2)	100 (76.3)	0.81
Male, n (%)	70 (24.3)	39 (24.8)	31 (23.7)	
Age	45.53 ± 13.15	46.78 ± 13.40	44.04 ± 12.73	0.07
Years of study				
Up to 9 years, n (%)	26 (9)	17 (10.8)	9 (6.8)	0.24
12 years or more, n (%)	262 (91)	140 (89.2)	122 (93.2)	
Monthly income				
Up to US$ 240.00, n (%)	156 (54.2)	85 (54.1)	71 (54.2)	0.99
More than US$ 240.00	132 (45.8)	72 (45.9)	60 (45.8)	
Clinical data				
Hospital admittance, n (%)	43 (14.9)	26 (16.5)	17 (12.9)	0.39
Time from onset symptoms	300.28 ± 201.30	329.16 ± 235.21	265.66 ± 144.42	0.45
Self-related symptoms				
Headache, n (%)	137 (47.6)	79 (50.3)	58 (44.3)	0.30
Ageusia, n (%)	129 (44.8)	66 (42)	63 (48)	0.30
Fatigue, n (%)	137 (47.5)	77 (49)	60 (45.8)	0.58
Dyspnoea, n (%)	65 (22.6)	39 (24.8)	26 (19.8)	0.31
Myalgia, n (%)	81 (28.1)	47 (29.9)	34 (25.9)	0.45
Chest pain, n (%)	49 (17)	30 (19.1)	19 (14.5)	0.30
Back pain, n (%)	63 (21.8)	35 (22.3)	28 (21.4)	0.85
Measured symptoms				
Anxiety (BAI) n (%)	179 (62.1)	74 (47)	105 (80)	0.000[#]
Olfactory disorder (CCRC), n (%)	148 (51.3)	66 (42)	82 (62)	0.0005[#]
Mild cognitive disorder (MoCA), n (%)	129 (44.7)	65 (41)	64 (48)	0.20

PSQI, Pittsburgh sleep quality index; BAI, Beck Anxiety Inventory; CCRC: Connecticut Chemosensory Research Center; MoCA: Montreal Cognitive Assessment. [#]Chi-square (p-value < 0.05).

by PSQI group n (%)/tested by PSQI group n (%), p-value 74 (47)/105 (80), 0.000], and olfactory disorder [non-tested by PSQI group n (%)/ tested by PSQI group n (%), p-value 66 (42)/82 (62), p-value 0.0005] were symptoms that were more frequently found among patients in the group tested by PSQI (Table 1).

The evaluation of sleep quality using PSQI was undertaken in patients with and without self-related sleep complaints, and the results show that n = 114 (89.06%) was bad sleepers (PSQI score > 5) and from these, n = 77 (60,15%) had a PSQI score > 10, that indicates severe difficulties for sleep. In patients with severe difficulties for sleep, the period until sleep onset was >60 min n = 47 (59.5), and their sleep durations were short (mean ± standard deviation no poor sleep quality/poor sleep quality 6.34 ± 1.31/4.92 ± 1.22, p-value 0.000). The administration of sleeping pills was reported by n = 38 (48%) of the patients with severe difficulties for sleep, and this group reported more problems keeping up with enthusiasm for daily activities [n (%) no poor sleep quality/poor sleep quality 35 (67.3)/75(95), p-value 0.000]. The self-reported reasons for trouble sleeping were due to getting up to use the bathroom n = 69 (87.3), having pain n = 60 (75.9), feeling too hot n = 58 (73.4), having bad dreams n = 52 (65.8), and not being able to breathe comfortably n = 49 (62) (Table 2).

Logistic regression analysis showed there was a significant odds ratio of poor sleep quality among women [OR (CI-95%) 1.93 (1–3.70), p-value 0.04] in univariate analysis, and [OR (CI-95%) 2.14 (1.01–4.51), p-value 0.04] in multivariate analysis. The prevalence of poor sleep quality was higher in patients with anxiety [OR (CI-95%) 8.19 (3.89–17.24), p-value 0.000] in univariate analysis, and [OR (CI-95%) 8.62 (3.89–19.12), p-value 0.000] in multivariate analysis. The olfactory disorder is associated with poor sleep quality [OR (CI-95%) 2.20 (1.19–4.07), p-value 0.01] in multivariate analysis (Table 3).

Discussion

In this cross-sectional study of 288 patients with long COVID and self-reported neurological symptoms, 131 (45.5%) patients had sleep complaints. Of these, 79 (27%) were diagnosed with poor sleep quality, according to PSQI. The group with poor sleep quality was mainly composed of women (between 44.04 ± 12.73 years), with ≥12 years of education and no related hospital admissions. Our analysis of the PSQI components showed that the group with poor sleep quality slept for fewer hours per night (4.92 ± 1.22/6.34 ± 1.31, p = 0.000) compared

TABLE 2 PSQI components of patients with sleep complaints by group (n=131).

	General (n =131)	PSQI score≤10 (n =52)	PSQI score>10 (n =79)	p-value
Time to fall asleep, *n* (%)				
<15 min, *n* (%)	15 (11.5)	11 (21.2)	4 (5)	**0.004**#
16–30 min, *n* (%)	31 (23.6)	24 (46)	7 (8.9)	**0.000**#
31–60 min, *n* (%)	33 (25.2)	12 (23)	21 (26.6)	0.65
>60 min, *n* (%)	52 (39.7)	5 (9.8)	47 (59.5)	**0.000**#
Hours of actual sleep (mean ± SD)	5.49 ± 1.43	6.34 ± 1.31	4.92 ± 1.22	**0.000***
Use of sleeping pills, *n* (%)	42 (32)	4 (7.7)	38 (48)	**0.000**#
Difficulties due to insomnia, *n* (%)				
Get to sleep within 30 min	114 (87)	40 (76.9)	74 (93.7)	**0.005**#
Staying awake during activities	99 (75.6)	38 (73)	61 (77.2)	0.58
Keep up enthusiasm	110 (83.9)	35 (67.3)	75 (95)	**0.000**#
Causes of insomnia, *n* (%)				
Wake up in the middle of the night	118 (90)	44 (84.6)	74 (93.7)	0.08
Get up to use the bathroom	107 (81.7)	38 (73)	69 (87.3)	**0.03**#
Have pain	88 (67.2)	28 (53.8)	60 (75.9)	**0.008**#
Feel too hot	71 (54.2)	13 (25)	58 (73.4)	**0.000**#
Have bad dreams	69 (52.7)	17 (32.7)	52 (65.8)	**0.000**#
Cannot breathe comfortably	70 (53.4)	21 (40.4)	49 (62)	**0.015**#
Cough or snore	63 (48)	20 (38.5)	43 (54.4)	0.07
Feel too cold	62 (47.3)	20 (38.5)	42 (53)	0.09
Others	76 (58)	24 (46)	52 (65.8)	**0.02**#

The bold values indicate the p-values with values minor or equal 0.05. PSQI: Pittsburgh sleep quality index. *Mann–Whitnney (p-value < 0.05), #Qui-quadrado (p-value < 0.05).

TABLE 3 The association between poor sleep quality and clinical features of the study population (n=288).

Clinical feature	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female	1.93 (1–3.70)	**0.04**	2.14 (1.01–4.51)	**0.04**
Hospitalization	0.91 (0.44–1.87)	0.80	0.82 (0.35–1.92)	0.64
Symptom onset (>6 months)	0.78 (0.44–1.39)	0.41	0.71 (0.37–1.36)	0.30
Fatigue	1.13 (0.63–2.00)	0.67	1.21 (0.58–2.50)	0.60
Dyspnoea	0.91 (0.49–1.70)	0.78	0.95 (0.44–2.02)	0.89
Anxiety (BAI)	8.19 (3.89–17.24)	**0.000**	8.62 (3.89–19.12)	**0.000**
Olfactory disorder (CCRC)	1.53 (0.91–2.55)	0.10	2.20 (1.19–4.07)	**0.01**
Ageusia	0.85 (0.51–1.43)	0.55	0.66 (0.36–1.29)	0.24
Mild cognitive impairment (MoCA)	1.09 (0.62–1.91)	0.75	1.39 (0.70–2.74)	0.34

The bold values indicate the p-values with values minor or equal 0.05. BAI, Anxiety Index; CCRC, Connecticut Chemosensory Research Center; MoCA, Montreal Cognitive Assessment.

to no poor sleep quality group, had a high frequency of sleep pills utilization [38 (48%)/4 (7.7), p = 0.000] and less enthusiasm to get things done [75 (95%)/35 (67.3), p = 0.000] than individuals with no poor sleep quality. The group with poor sleep quality had more anxiety and olfactory dysfunction symptoms than the group without sleep orders. In a regression analysis, anxiety [8.62 (3.89–19.12), p = 0.000], olfactory dysfunction [2.20 (1.19–4.07), p = 0.01] and female sex [2.14 (1.01–4.51), p = 0.04] were risks factors associated with poor sleep quality in this population.

The 27% prevalence of poor sleep quality in our sample group was consistent with those found in two reviews and meta-analysis studies involving post-COVID sequelae (27%) (Groff et al., 2021) and (32.9%) (Wu et al., 2021). Previous studies established that poor sleep quality is one of the most prevalent neurological symptoms among COVID-19 survivors, affecting approximately one-third of the population (Moura et al., 2022; Pinzon et al., 2022), particularly women, young people, and patients with mood disorders (Ahmed et al., 2021; Mendes Paranhos et al., 2022). A recent study showed that 73.8% of patients

with long COVID and poor sleep quality were women, and this sex difference in poor sleep quality may be associated with hormonal factors (Goweda et al., 2020). Furthermore, women tend to seek health services more regularly, possibly contributing to greater diagnosis in this group (Wang et al., 2013; Fernández-de-Las-Peñas et al., 2022).

In our analysis, the most affected PSQI components in the group diagnosed with poor sleep quality were difficulty initiating sleep, less sleep duration, administration of sleeping pills, nycturia, pain, nightmares, nocturnal breathing problems, feeling too hot, and less enthusiasm to get things done. It is well known that almost all of these components are associated with anxiety symptoms, which affect more than half of the population (Cutler, 2016; Oh et al., 2019). Long-term COVID-related poor sleep quality were associated with neuroinflammation and psychological disorders in a follow-up study with previously hospitalized patients with COVID-19 (Pellitteri et al., 2022). The patients were evaluated at 2 months (T1) and 10 months (T2) after discharge. The results showed the increased prevalence of insomnia of 10.6% in baseline to 27.3% at 10 months (T2), and a significant association between T2 PSQI total score and T2 anxiety levels, suggesting an association between poor sleep quality and psychological disorders over time.

Similar results were found in our univariate and multivariate logistic regression analyses, where poor sleep quality and anxiety in the sample population were associated with a higher odds ratio and could be correlated. These two symptoms were associated with high comorbidity in patients with long COVID. A comorbid mental health condition, such as anxiety and depressive disorders, affects 40% of patients with insomnia, and the onset of these conditions can be predicted by features listed in the diagnostic and statistical manual of mental disorders (DSM-5) (Roth, 2007; Huang and Zhao, 2020; Bard et al., 2023). Additionally, insomnia and anxiety have a hyperarousal pathogenetic mechanism caused by the dysregulation of neurotransmitter systems, including cholinergic and gamma-aminobutyric acid (GABA) (Blake et al., 2018). Hyperarousal and insufficient sleep disrupt the corticolimbic circuitry function, impairing affective reactivity and regulation (Riemann et al., 2010).

The higher odds ratio in our study, which could indicate the correlation between the two objectively measured outcomes of olfactory dysfunction and the occurrence of poor sleep quality in the patients evaluated, was a significant finding. These sleep and olfactory disturbances are commonly associated with various pathologies, including Alzheimer's disease, Parkinson's disease, schizophrenia, and depression (Barresi et al., 2012). In context of COVID-19 patients, recent studies involved neuroimaging found functional and structural changes in long COVID patients with persistent olfactory dysfunction such as presence of microhemorrhages at olfactory bulb (Aragão et al., 2020) and olfactory bulb edema (Laurendon et al., 2020); reduced tissue perfusion in the orbital and medial frontal regions (Yus et al., 2022); decreased in grey matter (GM) volume and increased in mean diffusivity in olfactory related regions (Wingrove et al., 2023); increased in functional connectivity (FC) between the left orbitofrontal cortex (OFC), visual association cortex and cerebellum and reductions between the right (OFC) and dorsal anterior cingulate cortex (Campabadal et al., 2023). These data support the hypothesis that persistent olfactory dysfunction may reduce attentional processing towards olfactory stimuli and perhaps the sustained lack of olfactory attention or sensing underlies, which might explain why some COVID-19 patients have not recovered their sense of smell, and olfactory impairment as a potential biomarker of subsequent neurodegeneration (Campabadal et al., 2023).

A wide variety of information captured in the waking period depends on sleep to be consolidated, including sensory memory (Barnes and Wilson, 2014). Previous findings regarding smell have shown that sleep favours changes in olfactory cortical circuits contributing to the strength and precision of odour memories and perception (Miyamoto et al., 2009; Barnes and Wilson, 2014). During sleep, especially during slow-wave sleep (SWP), the piriform cortex becomes hypo-responsive to environmental odour stimulation. It enhances functional connectivity between other cortical regions and the limbic system, compared to the waking state (Günbey et al., 2015). For example, a common behavioural response in many mammals is post-prandial sleep, which contributes to the memory of odours and flavours of consumed food (Yokoyama et al., 2011). Poor sleep quality are integral part of complex changes related to long COVID and should be part of the patient's clinical management.

In our findings cognitive impairment in long COVID patients (assessed by MoCA) was not associated with sleep problems. A previous study with a more comprehensive neuropsychological protocol showed that cognitive performance was correlated with olfactory dysfunction, PSQI had moderate correlations with processing speed and letter fluency, anxiety to a lesser extent, but not depression. The authors argue that cognitive disorder is not secondary to psychological aspects, consistent with our results (Delgado-Alonso et al., 2022).

This study has some limitations. First, the single-center cross-sectional design of the study limits the generalisability of the data, and all inferences about causality and effect are hypothetical. Moreover, the absence of formal data regarding previous clinical history and the acute phase of COVID-19 is a potential confounding factor, which was minimized by carefully using an anamnesis form and specialized consultation with neurologists. The self-related symptoms, including sleep orders and other limitations. These were assessed in the search form and were part of a qualitative sample characterisation. The use of quantitative tools is necessary for more precision. Future follow-up and intervention studies should be conducted to monitor this population and assess the effectiveness of treatments. From a clinical point of view, we recommend screening patients with acute and post-acute COVID-19 for poor sleep quality associated with mood disorders and olfactory dysfunction to improve appropriate treatment. The use of polysomnography to monitor and assess any potential obstructive respiratory events that might affect sleep quality is recommended.

Conclusion

A high prevalence of individuals with long-term poor sleep quality was observed in this cohort of patients with long COVID and associated neurological symptoms, such as anxiety and olfactory

dysfunction. Our results highlight the need to continue monitoring the rate of associated neurological symptoms in long COVID over time. Furthermore, clinical trials and longitudinal studies are recommended to verify the effectiveness of potential treatments and the postulated risk for an increase in neurodegenerative disorders in this population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa com Seres Humanos do Centro de Ciências Biológicas e da Saúde, Universidade do Estado do Pará. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AP, AD, GS, JQ, and LF: design and conduct of the study. AP, AC, TB, AR, KS, LD, LS, MM, CO, MD, and GK: collection, management, analysis, and interpretation of the data. GS, JQ, LF, PV, AP, and AD: preparation, review, or approval of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuropsychiatric consequences of COVID-19 related olfactory dysfunction: could non-olfactory cortical-bound inputs from damaged olfactory bulb also contribute to cognitive impairment?

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Introduction

Disturbances in smell emerged at the very beginning of the pandemic as the predominant neurological symptom of COVID-19 (Boscolo-Rizzo et al., 2020; Menni et al., 2020) providing evidence of COVID-19 related neurological abnormalities originating from pathology of the olfactory epithelium. The very first prospective imaging studies (MRI scans 3–4 months after COVID-19 hospitalization in Wuhan) reported significant changes in gray matter volume correlated with loss of smell and memory loss, primarily found in cingulate gyrus, piriform cortex, and hippocampus (Lu et al., 2020). Since then, the available data have substantially expanded and the focus shifted to long-term sequelae in which cognitive and mental functioning are prominently featured in post-COVID and long-COVID conditions [see rev. (Rogers et al., 2020; Xydakis et al., 2021; Batiha et al., 2022; Doty, 2022; Hasegawa et al., 2022; Kay, 2022; Lippi et al., 2023)]. Research in this area is rapidly progressing; the most recent articles are being collected in this Special Issue underlining that investigation of the neuropsychiatric sequelae of olfactory dysfunction related to COVID-19 infection is particularly critical to characterize the pathological effects of COVID-19 on brain function and to develop strategies to improve patient's quality of life and mental wellbeing.

In this paper we call attention to potential benefits these studies may gain from a wider approach, including respiratory related oscillations (RRO) in forebrain structures induced by rhythmic nasal airflow. It may help in two major aspects of this research, concerning the two "ends" of the pathology of the central olfactory processing networks, extending from the olfactory bulb (OB) all the way to cortical networks (Xydakis et al., 2021). These are two points where processing of distinct sensory inputs from the OB significantly overlaps and where investigating RRO mechanisms may help to understand (1) how smell loss is caused by SARS-2-COV infection which does not directly attack olfactory sensory neurons (OSN) (Cooper et al., 2020; Iadecola et al., 2020; Doty, 2022; Las Casas Lima et al., 2022; Rodriguez-Sevilla et al., 2022; Butowt et al., 2023) and (2) how olfactory dysfunction advances to a complex condition of diverse cognitive and emotional disturbances (Putri et al., 2021; Soltani et al., 2021; Vanderlind et al., 2021; Batiha et al., 2022; Kay, 2022; Crook et al., 2023).

Respiratory rhythmic modulation of a wide range of cognitive functions has been reported both in rodents and human, from sensory processing and motor coordination to various memory functions [rev. (Heck et al., 2019)]—i.e. not directly related to gas exchange. In rodents, during exploration associated with sniffing, respiratory rate accelerates to match the frequency of hippocampal (HPC) theta rhythm, an intrinsic brain oscillation. During these episodes, RRO play a key role in synchronizing sensory sampling in OB on one hand and rhythmic fluctuations in excitability of neurons involved in central processing in HPC and piriform cortex, on the other. Outside of sniffing episodes, when respiration is in the delta range, OB RRO synchronize instead with frontal cortical delta oscillations. In rats and mice, these waking delta oscillations include task-related intrinsic oscillations (Fujisawa and Buzsaki, 2011; Dejean et al., 2016; Karalis et al., 2016; Furtunato et al., 2020) and are markedly different from the broad-band thalamo-cortical delta rhythms of deep sleep (Pittman-Polletta et al., 2018), being spectrally narrow-band, cortically generated, hierarchically nested with gamma oscillations (Hunt et al., 2017; Pittman-Polletta et al., 2018), and associated with various cognitive functions (Nacher et al., 2013; Hall et al., 2014; Riecke et al., 2015; Hunt et al., 2017). Since respiration is slower in humans than rodents, whereas the frequencies of brain rhythms are evolutionary wellpreserved (Buzsaki and Draguhn, 2004), RRO in humans exhibit a different form of coupling with forebrain oscillations. It periodically modulates the levels of oscillatory activity in forebrain circuits, including both "slow" delta and theta rhythms as well as "fast" beta and gamma rhythms activity known to be involved in cognitive processes (Zelano et al., 2016). Data demonstrating the potential role of RRO in cognitive processing has accumulated in recent years also from human studies (Zelano et al., 2016; Arshamian et al., 2018; Perl et al., 2019). In humans, behaviors modulated by respiratory phase include eye (Rittweger and Popel, 1998; Rassler and Raabe, 2003) and finger (Ebert et al., 2002; Nassrallah et al., 2013) movements, visual (Li et al., 2012)and auditory (Gallego et al., 1991)reaction times, grip-force (Li and Laskin, 2006), olfactory memory consolidation (Arshamian et al., 2018), aversive associative learning (Waselius et al., 2019), visuospatial cognition (Perl et al., 2019), and visual working memory retrieval (Nakamura et al., 2018).

The strategic use of brain oscillations as a mesoscale mechanistic link between cellular and circuit-level neurophysiology and brain-wide network activity giving rise to cognition and behavior has borne fruit in research on schizophrenia (Siok et al., 2006; Ford et al., 2007; Hajos et al., 2008; Lanre-Amos and Kocsis, 2010; Kocsis, 2012; Driesen et al., 2013; Harvey et al., 2013; Kocsis et al., 2013, 2014; Khlestova et al., 2016; Pittman-Polletta et al., 2018; Parker et al., 2019; Hamilton et al., 2020; Thorn et al., 2022), Parkinson's disease (Brown, 2003; Oswal et al., 2013; Little and Brown, 2014; Li and Zhang, 2015; Johnson et al., 2021), and many other pathological conditions, e.g., epilepsy (Buzsaki et al., 1990; Steriade, 2005; Beenhakker and Huguenard, 2009; Takeuchi and Berenyi, 2020), autism (Ben-Ari, 2015; Casanova et al., 2020; Kayarian et al., 2020; Jia et al., 2021), dyslexia (Hancock et al., 2017; Vidyasagar, 2019), and neurodegeneration (Rossini et al., 2007; Nimmrich et al., 2015). The functions, dynamics, and key features including characteristic frequencies of brain oscillations are similar in humans and rodents, and they have been shown to be not only robust but heritable (van Pelt et al., 2012) and responsive to interventions, making them a valuable tool for translational research.

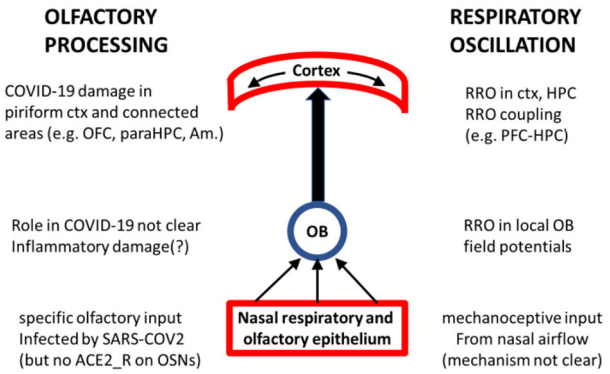

FIGURE 1
Schematics of key nodes of the olfactory processing system **(middle)** with their involvement in COVID-19 **(left)** and in RRO **(right)**. Olfactory and respiratory epithelium plays crucial role in generating both signals and is the primary site of SARS-CoV-2 infection. OB is transmitting ascending olfactory sensation as well as mechanoceptive signal of rhythmic nasal airflow and is receiving "top-down" information related to olfactory processing (from ctx, HPC, Amygdala) as well as oscillatory drive (e.g. theta, gamma from HPC); reports of its possible COVID-19 inflammatory damage are not fully consistent (Sherif et al., 2022; Abdou et al., 2023; Muccioli et al., 2023). Piriform cortex is the primary target of the olfactory tract where cortical processing of olfactory information involves RRO-driven local gamma oscillations (Gonzalez et al., 2023) and is transmitted to other cortical structures, oscillatory coupled at different frequencies [including RRO (Mofleh and Kocsis, 2021a)], for further processing in the context of different cognitive functions. COVID-19 impairment of these cortical structures is well-documented.

We believe that RRO may provide mechanistic insight into both ends of COVID-19 related olfactory dysfunction, shedding light on both questions posed above (see Figure 1) and may be important for investigations of olfactory processing in general and its COVID-19 related pathology, in particular. RRO adheres to the principle of hierarchical organization of brain oscillations in which slow rhythms (delta, theta, alpha, etc.) modulate local gamma oscillations to facilitate functional coupling of local and distant networks. Gamma is present in all cortical networks and in the OB (Beshel et al., 2007; Brea et al., 2009), as well. RRO couples with slow rhythms intrinsically generated in cortical networks (Kocsis et al., 2018; Mofleh and Kocsis, 2021a) and modulates cortical gamma (Cavelli et al., 2020; Gonzalez et al., 2023). It was recently shown that RRO-gamma coupling in the piriform cortex acted to select and amplify the best set of neurons for representing the odor sensed during a sniff, and to quieten less relevant neurons (Gonzalez et al., 2023), pointing to the strong involvement of RRO in olfactory processing at every level of organization from the OB to higher structures (Figure 1). Thus, our hypothesis concerning RRO does not suggest a separate channel to COVID-19 pathology, alternative to olfactory disfunction. It may rather suggest that considering RRO may provide a significant

contribution to investigations of the neuropsychiatric sequelae of olfactory dysfunction related to COVID-19 infection. This latter is rapidly progressing, extending rigorously designed longitudinal MRI studies (Douaud et al., 2022) to comparing COVID-19 patients with or without olfactory dysfunction (Delgado-Alonso et al., 2022; Yus et al., 2022; Caroli et al., 2023) and alterations in functional connections between parahippocampal gyrus and orbitofrontal cortex or other brain regions associated with sensory processing and cognitive functioning in groups of healthy controls, vs. COVID-19 with vs. without smell loss (Díez-Cirarda et al., 2022; Wingrove et al., 2023). Below, we describe the potential links between RRO and cognitive function and dysfunction, and between olfactory dysfunction and impaired RRO (about which less is known), in greater detail.

Non-olfactory RRO input from OB is strongly involved in cortical processing and cognitive function

Large potential waves in OB and piriform cortex rhythmically occurring at each inspiration have been demonstrated over 80 years ago (Adrian, 1942) and adjustment of the respiratory rate to the frequency of HPC theta rhythm, invariably present during stereotyped sniffing bouts, was reported several decades later (Macrides, 1975; Macrides et al., 1982; Semba and Komisaruk, 1984). These findings initiated highly productive research clarifying the cellular mechanisms involved, how they are adapted to different behaviors and cognitive tasks, and how they are affected by numerous pharmacological compounds [rev. (Klemm, 1976; Kepecs et al., 2006; Kay et al., 2009; Kay, 2014; Tort et al., 2018a; Heck et al., 2019)]. As a result, the vital engagement of HPC in olfactory processing is well established. Theta rhythm generated in HPC controls multiple processes in the olfactory system from the OB (Kepecs et al., 2006; Rojas-Libano et al., 2018; Liu et al., 2020) to the piriform cortex in both rodents (Wilson et al., 2011; Xu and Wilson, 2012; Morrison et al., 2013; Kay, 2014; Trieu et al., 2015; Dupin et al., 2020; Iravani et al., 2021; Sheriff et al., 2021; Poo et al., 2022) and human (Jiang et al., 2017; Iravani et al., 2021; Yang et al., 2022). Theta rhythm from HPC also synchronizes the olfactory system with multiple non-olfactory sensory channels and associated motor control of rhythmic nasal, whisker, and head movements to further optimize odor perception. Thus, theta rhythm synchronized with RRO occupies a central position in a complex system considered a "paradigmatic example" of active sensing (Wachowiak, 2011; Corcoran et al., 2018) aimed at processing synchronized streams of olfactory and other (e.g. tactile, visual, etc.) information.

More recently, an explosion of findings firmly demonstrated that brain activity and cognitive function are also modulated by respiratory rhythm outside of sniffing episodes, as well [rev. (Tort et al., 2018a; Heck et al., 2019)]. Slow, non-theta RRO were detected in numerous brain structures, including higher order cognitive centers as the prefrontal cortex (Biskamp et al., 2017; Zhong et al., 2017) and HPC (Yanovsky et al., 2014; Chi et al., 2016; Lockmann et al., 2016). RRO coupling with wide-spread forebrain activity was confirmed using advanced techniques, including single unit firing (Rojas-Libano and Kay, 2008; Chi et al., 2016; Biskamp et al., 2017; Zhong et al., 2017; Koszeghy et al., 2018; Jung et al., 2022, 2023), current source density (Rojas-Libano and Kay, 2008; Chi et al., 2016; Lockmann et al., 2016), and phase modulation of local gamma activity (Ito et al., 2014; Biskamp et al., 2017; Zhong et al., 2017; Rojas-Libano et al., 2018; Cavelli et al., 2020). It was firmly established that RRO derives from rhythmic nasal airflow in the OB (Yanovsky et al., 2014), which dynamically couples with intrinsic network oscillations in higher brain structures (Kocsis et al., 2018) either: (1) by coherence, when the frequency of RRO matches that of local field potentials such as delta and theta activity in rodents (Ito et al., 2014; Yanovsky et al., 2014; Chi et al., 2016; Lockmann et al., 2016; Biskamp et al., 2017; Tort et al., 2018b), or (2) by phase-amplitude modulation when the frequencies diverge, as in gamma high frequency oscillations (HFO; >100 Hz) in rodents (Ito et al., 2014; Yanovsky et al., 2014; Biskamp et al., 2017; Zhong et al., 2017) or all characteristic EEG rhythms in human (which have frequencies comparable to those in rodents, but faster than human respiration) (Zelano et al., 2016).

Importantly, the effect of RRO driven by mechanoceptive input from the OB goes well beyond rhythmic modulation of the level of activity in higher brain structures; it is deeply involved in complex circuit mechanisms of neural network function. This is an area of intense on-going investigations on different levels of network organization, from cellular to interregional communication (Rojas-Libano and Kay, 2008; Ito et al., 2014; Chi et al., 2016; Lockmann et al., 2016; Biskamp et al., 2017; Zhong et al., 2017; Koszeghy et al., 2018; Rojas-Libano et al., 2018; Cavelli et al., 2020; Mofleh and Kocsis, 2021a; Jung et al., 2022, 2023; Gonzalez et al., 2023). Although OB projection to different higher brain regions is not direct (Hoover and Vertes, 2007; Mori et al., 2013; Yanovsky et al., 2014; Moberly et al., 2018), mostly mediated by the piriform cortex, RRO appears in functionally different areas dynamically coupled in a complex behavior- and task-related manner. As RRO depends on vigilance state (Girin et al., 2020; Mofleh and Kocsis, 2021a), it appears coincident with various state-dependent intrinsic brain oscillations which exhibit characteristic spatial distributions. For example, transient time windows of long-range cortico-cortical coupling of gamma activity (a phenomenon implicated in visual perception, attention, and bottom-up information transfer) are regularly evoked at a specific time during each breathing cycle, as high frequency oscillations e.g. in the frontal cortex are phase-coupled with OB and consequently with piriform cortex (González et al., 2023). Frontal cortex and HPC, typically generating delta and theta oscillations, respectively, are accessible for rhythmic OB input depending on the behavior-dependent respiratory rate, and this has strong implications for their communication. We have shown recently that in resting states, slow (∼2 Hz) respiration firmly couples with frontal cortex providing a delta communication channel toward HPC with weaker and variable RRO (Mofleh and Kocsis, 2021a,b)—i.e. in contrast with the well known dominant theta-driven communication controlled by HPC during exploration. In association areas, e.g. in parietal cortex (recorded far caudal from primary olfactory areas) where RRO and intrinsic brain oscillations are driven by converging extrinsic inputs transmitted from different sources, the two rhythms may simultaneously activate partially overlapping cellular populations

at different strengths depending on vigilant states, even though the laminar profiles of theta and RRO diploes (a different level of organization) are in different layers (Jung et al., 2022, 2023).

COVID-19 mechanisms in the olfactory epithelium, affecting smell and possibly RRO

Potential pathomechanisms of COVID-19 related olfactory dysfunction have been extensively studied and regularly reviewed in the past several years. At the very beginning (Summer of 2020) for example, Cooper et al. (2020) pointed out, that the natural history of COVID-19-associated anosmia argues that SARS-CoV-2 attacks the olfactory system through mechanisms distinct from those used by the more benign endemic coronaviruses (Giacomelli et al., 2020; Spinato et al., 2020). In fact, imaging studies of the olfactory bulb in COVID-19 patients were either normal or revealed focal inflammation (Eliezer et al., 2020). According to current understanding, SARS-CoV-2 does not directly infect OSNs; COVID-19 induced OSN dysfunction is mediated instead by alterations to the microenvironment maintained by angiotensin converting enzyme-2 (ACE2) receptor-expressing cells in the olfactory epithelium [rev. (Cooper et al., 2020; Iadecola et al., 2020; Las Casas Lima et al., 2022; Rodriguez-Sevilla et al., 2022; Butowt et al., 2023)]. It is believed that the primary target of SARS-CoV-2 infection in the olfactory mucosa are sustentacular cells, known to express ACE2 receptors (Bilinska and Butowt, 2020; Bilinska et al., 2020; Brann et al., 2020; Fodoulian et al., 2020; Klingenstein et al., 2020; Ye et al., 2021; Shahbaz et al., 2022). Moreover, the virus was demonstrated directly in these cells while still replicating in COVID-19 patients who died a few days after infection (Khan et al., 2021).

Rodent sustentacular cells have been ascribed myriad roles collectively referred to as "supporting": absorptive, detoxifying, metabolic, nourishing, phagocytic, physical, secretory, structural (Getchell et al., 1989; Hansel et al., 2001; Kam et al., 2014; Liang, 2020; Butowt and von Bartheld, 2021; Khan et al., 2021). The tight anatomical and functional links between OSNs and sustentacular cells is a strong indication that impairment of the latter would affect the function of the former. Through changes in extracellular ionic concentrations, nutrient bioavailability, or structural support, alterations in the microenvironment of OSNs could easily cause disruptions in both the perception of odorants and the synchronization of brain-wide electrical activity. The cellular mechanisms of RRO generation in the OB are not yet clear at this level of detail, and we are not aware of published research on whether impaired RRO are associated with COVID-19 pathology. But it seems plausible that impaired function of non-sensory olfactory epithelial cells may negatively affect RRO. Indeed, the potential for metabolic factors to instigate changes in brain rhythms has been demonstrated, e.g., in recent biophysical models of burst suppression under propofol anesthesia (Ching et al., 2012) and the sleep-stage architecture of thalamocortical spindles (Roberts, 2007).

The causal relationship between OSN dysfunction and potential dysrhythmias is not clear *a priori*. Disruption of OSN function might directly lead to impaired RRO, as OSNs can respond not only to odorants but also to mechanical stimuli (Connelly et al., 2015; Grosmaitre et al., 2021) and transmit both odor and air flow-driven mechanical signals (Carey et al., 2009; Iwata et al., 2017). Such mechanosensory activity has been extensively studied as a mechanism in sniffing-related synchronization of brain activity. However, its role in the generation of lower (i.e., delta) frequency RRO targeting a wider range of forebrain regions remains unidentified. In the opposite direction, mechano-sensation of rhythmic airflow and its deficits (i.e., the disorganization of RRO) may directly affect odor perception already at the level of OB. Odor encoding occurs relative to the phase of respiration (Kepecs et al., 2006; Cury and Uchida, 2010), i.e. during inhalation, and its frequency determines many aspects of OB activity (David et al., 2015; Short et al., 2016). Olfactory external tufted cells exhibit rhythmic bursting activity in several frequency ranges synchronized within olfactory glomeruli (Hayar et al., 2004; De Saint Jan et al., 2009) by multiple mechanisms including gap junction connectivity, slow (dendritic) excitatory currents, and slow recurrent inhibition from periglomerular cells (Hayar et al., 2005), and most likely mediate the phase-locking of OB output to respiration (Buonviso et al., 2003). Thus, impaired RRO may directly contribute to COVID-19 associated olfactory deficits.

Discussion

In this opinion paper we advocated for the investigation of potentially impaired non-olfactory inputs arising from the olfactory epithelium and involved in cognitive function (e.g., RRO) as a potential mechanistic factor underlying the neuropsychiatric consequences of SARS-CoV-2 infection and linking them to COVID-19 related olfactory dysfunction. We should mention however, that long-Covid is a new and very complex condition, which includes many mechanisms—viral, inflammation, signaling pathways and, of course, non-homogeneous, depending on the acute phase, virus & patients particularities. RRO is one potential component in this puzzle that should be considered.

Additionally, given the well established links between olfactory function and mental health, RRO are likely to play a significant role in other medical conditions (MacKay et al., 2018) as well, when these oscillations may be disrupted for different reasons, or when this extrinsic synchronizing input remain functional while intrinsic brain oscillations are disturbed. An obvious example of the first, besides impairments of the olfactory epithelium, is the condition of long-term intubation, necessary in the context of a variety of medical indication and treatment. Its potential consequences on cognition are hard to distinguish from those directly related to the basic pathology. However, promoting RRO in sensory and motor cortex through the activation of oro-facial and neck muscle activity in synchrony with respiration (Wachowiak, 2011; Corcoran et al., 2018) may have therapeutic benefits for both weaning procedures prior to extubation, and subsequent rehab. As for the second possibility, abnormal brain oscillations, "oscillopathies", are commonly found in a wide variety of psychiatric diseases associated with severe cognitive deficits (see e.g. Katsuki et al.,

2022; Shu et al., 2022; Sohal, 2022; Syed et al., 2022; Beste et al., 2023; Ramos et al., 2023; Wischnewski et al., 2023 for recent reviews). Rhythmic nasal airflow continues uninterrupted, but the potential alterations to the functionality of cortical RRO remain unclear. We have shown recently for example that normal RRO patterns (Mofleh and Kocsis, 2021a,b) remain functional after severe disruption of intrinsic cortical and HPC oscillations under the psychotomimetic Ketamine, in a state characterized by "psychotic-like" behavior and abnormal cortical gamma activity, even with a highly unstable respiratory rate (Staszelis et al., 2022). Whether and to what extent this source of extrinsic oscillatory drive provides a mechanism for interregional long-range oscillatory coupling between cortical networks requires further investigations in specific disorders.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Olfaction and neurocognition after COVID-19: a scoping review

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Introduction: COVID-19 induces both acute and chronic neurological changes. Existing evidence suggests that chemosensory changes, particularly olfactory loss, may reflect central neurological dysfunction in neurodegenerative diseases and mark progression from mild cognitive impairment to Alzheimer's. This scoping review summarizes the available literature to evaluate the relationship between neurocognition and olfaction in young to middle-aged adults with minimal comorbidities following COVID-19 infection.

Methods: A literature search of PubMed, Ovid Embase, Web of Science, and Cochrane Library was conducted. Studies underwent title/abstract and full text screening by two reviewers, with a third reviewer resolving any conflicts. Remaining studies underwent data extraction.

Results: Seventeen studies were eligible for data extraction after the review process, where 12 studies found significantly poorer cognition in those suffering from olfactory dysfunction, four studies showed no association between cognition and olfaction, and one study reported lower anosmia prevalence among patients with cognitive impairment.

Conclusion: The majority of studies in this review find that olfactory dysfunction is associated with poorer cognition. More rigorous studies are needed to further elucidate the relationship between olfaction and cognition after COVID-19.

KEYWORDS

COVID, neurocognition, olfaction, review, PASC

1. Introduction

The COVID-19 pandemic propelled olfactory dysfunction to the forefront of otolaryngology research (Hopkins, 2022). Early investigations have provided preliminary insight into the mechanisms by which COVID-19 acutely affects the olfactory system and whether olfaction provides a window into greater neurological dysfunction caused by the virus (Butowt and Bartheld, 2021; Zazhytska et al., 2022). In addition to neurological disturbances of chemosensation, there are numerous reports of other neurological deficits as part of long COVID, also referred to as post-acute sequelae of COVID-19 (PASC). In particular, neurocognitive deficits, frequently referred to as "brain fog," can persist for more than a year in subsets of patients (Zhou et al., 2020; Hugon et al., 2022; Asadi-Pooya et al., 2023). While many patients report experiencing post-COVID brain fog or memory problems, it is important to note

that there are indeed quantifiable structural changes to several areas in the brain (e.g., crus II, cognitive cerebellar lobule) which are associated with greater degrees of cognitive decline in SARS-CoV-2-positive individuals (Douaud et al., 2022). Given that there are discrete structural changes observed in the brain after COVID-19, it is possible that such changes are responsible for specific, measurable cognitive deficits encapsulated within the patient experience of PASC.

The study of olfaction as a biomarker of neurological dysfunction is not new: a body of literature exists that examines the relationship between olfaction and cognitive decline in elderly populations, though studies have shown mixed results. A systematic review found the presence of an association between onset of Alzheimer's Disease (AD) and olfactory function but highlighted significant variability of study rigor and olfactory testing methodology (Sun et al., 2012). Additionally, the study demonstrated a paucity of prospective, longitudinal study data, calling for further investigation into olfactory testing as a screening tool for AD or mild cognitive impairment (MCI). A recent study showed no statistically significant differences in Sniffin' Sticks identification scores between individuals with subjective cognitive decline, MCI, and AD (Pusswald et al., 2023).

However, the effects of post-infectious smell loss on neurocognition is not well characterized. The association between olfaction and varying degrees of cognitive impairment are well-documented in the literature among an elderly population; however, as COVID-19-associated olfactory changes are often observed in healthy adults without neurodegenerative changes, synthesizing the body of literature that examines olfaction in healthy young adults is required. Understanding the relationship between olfaction and neurocognition in this population will provide a basis for better understanding the underlying neural processes at work in COVID-19 patients with olfactory changes. Given the associations between olfaction, neurocognition, and COVID-19, we sought to elucidate whether available literature supports olfaction as a biomarker for broader neurological disturbances in PASC among non-elderly, otherwise healthy adults following COVID-19.

2. Materials and methods

A systematic literature search of PubMed, Ovid Embase, Web of Science, and Cochrane Library was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines (PRISMA-ScR) to capture all studies investigating cognitive outcomes associated with COVID-19-related olfactory dysfunction (Tricco et al., 2018). The search queries used to obtain relevant articles are included in Appendix A.

Articles met inclusion criteria if they were written in English, included adults 18–60 years of age, and examined the associations between olfaction and cognition among a population affected by COVID-19. Articles were excluded if they solely examined a pediatric population ages <18 or elderly population > 60 years, studied individuals with pre-existing neurodegenerative diseases, or were review articles, commentaries, letters to the editor, or conference abstracts. To identify relevant articles, titles and abstracts of each article were screened by two reviewers (BV, PJ, JT, or NW). Articles meeting inclusion criteria after title and abstract review were then screened with full text review by two reviewers. Any disagreements on initial title and abstract or full text review were resolved by a third reviewer that did not perform the initial review. A PRISMA-style flow diagram was generated using Covidence systematic review management software. All articles that passed the full text review then underwent data extraction (Table 1). The primary outcome of interest was the association between olfactory dysfunction related to COVID-19 and cognitive measures. Other data that were extracted from the articles included study author, year published, method of olfaction assessment, method of cognition assessment, and demographic characteristics of patients.

3. Results

3.1. Review process

We conducted our systematic review of available literature in January 2023, which yielded 2,466 articles. Removal of 1,166 duplicates resulted in a total of 1,300 articles for title and abstract screening. Of these, 108 articles moved on to full text and bibliographic reference review, where 91 studies were excluded for the following reasons: wrong language, wrong population age, wrong study design or publication type, failure to include assessment of olfaction or cognition, and failure to directly analyze the association between olfaction and cognition. Conclusion of this process resulted in 17 studies eligible for data extraction and inclusion in our review. Figure 1 illustrates the PRISMA-style flow chart documenting the study screening process.

3.2. Study participants

All studies that underwent data extraction include young to middle-aged adults. Notably, all but three of these studies included cohort population results for elderly adults; a single study included at least one adolescent in addition to the target population. Twelve studies have more females than males; and, among studies reporting explicit ages, the mean age of the extracted population data range from 35 to 67.23 with standard deviations ranging from 8.9 to 15.46.

3.3. Assessment of olfaction

Methods for assessing olfaction included both subjective self-report and psychophysical (semi-objective) assessments of olfaction. Subjective methods were survey (12/17 studies) and chart review (1/17 studies). Seven studies incorporated psychophysical assessment methods, including Brief Smell Identification Test (BSIT) (2/17 studies), University of Pennsylvania Smell Identification Test (UPSIT) (2/17 studies), Sniffin' Sticks (2/17 studies), and *Test Olfactif informatisé pour le Diagnostic de la maladie d'Alzheimer et de l'Apathie* (TODA) (1/17 studies). Only one study lacked experimental groups composed of both patients with and without smell dysfunction. A single study had an experimental group composed of only individuals with qualitative smell changes (Kopishinskaia et al., 2021). Most studies examined primarily quantitative smell loss, while three studies assessed qualitative smell alteration.

Of the 17 studies included in the review, 11 studies utilized subjective reports only to assign olfactory status. Among the studies using subjective reports as the measure of olfactory function, three studies did not find any significant difference in cognition between

TABLE 1 Data extracted from included studies.

Authors, year	*n*, gender	Mean age±SD, range	Olfactory assessment methods	Cognition assessment methods	Olfactory results	Cognition results timepoint	Relationship between olfaction and cognition
Alemanno et al. (2021)	87, 25 female	67.23 ± 12.89	Survey	MMSE, MoCA	18/87 had anosmia	Acute respiratory intervention:*intubation:* 74.2% had MoCA deficit, higher than Venturi mask ($p = 0.005$); 12.9% had MMSE deficit, higher than Venturi mask ($p = 0.024$) *BIPAP:* 94.4% had MoCA deficit, 55.6% had MMSE deficit *Venturi mask:* 77.8% had MoCA deficit, 48.3% had MMSE deficit *no O_2:* 77.8% had MoCA deficit, 44.4% had MMSE deficit	No significant differences in cognitive functions between anosmics and non-anosmics
Almeria et al. (2020)*	35, 19 female	47.6 ± 8.9, 24–60	Retrospective chart review	Digit span (backwards)	20/35 had anosmia	45.7 ± 7.5, 30.0–57.5	Anosmics had lower scores ($t = 2.259$, $p = 0.031$)
Azcue et al. (2022)	73, 51 female	44.36 ± 9.47, 18–85	BSIT	MoCA, SPCT, SDMT, HVLT-R, BVMT-R, TMT, Benton JLO	53 normal (9.96 ± 0.99), 3 relatively abnormal (7.67 ± 0.58), 15 abnormal (6.47 ± 0.99)	MoCA 25.09 ± 3.06; SPCT-3 16.75 ± 5.26; SDMT 47.23 ± 10.93; HVLT-R trial 1 5.31 ± 1.55, total 22.57 ± 5.92, trial 4 7.90 ± 2.83, DI 9.53 ± 2.47; BVMT-R trial 1 5.63 ± 3.54, trial 1–3 22.38 ± 7.37, trial 4 8.31 ± 2.70, DI 5.64 ± 1.04; TMT-A 38.41 ± 14.50; Benton JLO 24.52 ± 4.98	BSIT showed significant positive correlation with MoCA, SPCT-3, SDMT, HVLT-R trial 1–3, BVMT-R discrimination index, and Benton JLO and significant negative correlation with TMT-A. Participants with abnormal BSIT had significantly worse general cognition, attention, verbal memory, visual memory, visuospatial perception, and abstraction capacity.
Cacciatore et al. (2022)	83, 20 females	66.9, 95% CI: 64.2–69.7	Survey	MoCA	15/83 had hyposmia/ hypogeusia	Mean 24.1, range 23.4–24.8	No significant correlation between cognition and hyposmia/hypogeusia
Caspersen et al. (2022)	774, 449 female	25–65+	Survey	Survey	COVID-19 dx 11–12 months ago: 28 had altered smell or taste COVID-19 dx 1–6 months ago: 128 had altered smell or taste	COVID-19 dx 11–12 months ago: 30 had poor memory, 20 had brain fog COVID-19 dx 1–6 months ago: 81 had poor memory, 84 had brain fog	No significant correlation between altered smell or taste and poor memory or brain fog
Cecchetti et al. (2022)	49, 13 females	60.8 ± 12.6	Survey	Phonemic fluency, SDMT, RAVLT immediate recall	22/49 had dysgeusia/hyposmia during acute COVID-19	baseline: phonemic fluency 27.9 ± 10.2, SDMT 35.1 ± 1.9, RAVLT 29.3 ± 9.4 follow up: phonemic fluency 31.9 ± 11.4, SDMT 41.8 ± 1.3, RAVLT 35.8 ± 11.2	Those with dysgeusia/hyposmia had less RAVLT (immediate recall memory) improvement; no significant difference in improvement on phonemic fluency or SDMT

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TABLE 1 (Continued)

Authors, year	*n*, gender	Mean age±SD, range	Olfactory assessment methods	Cognition assessment methods	Olfactory results	Cognition results timepoint	Relationship between olfaction and cognition
Chen et al. (2022)	200, 129 females	44.6 ± 15.46, 19–82	Survey, UPSIT	MoCA, NIH Toolbox	Survey: 109/200 had smell changes UPSIT: 53/164 had normosmia, 62/164 had mild hyposmia, 32/164 had moderate hyposmia, 13/164 had severe hyposmia, 4/164 had anosmia	102/191 had normal MoCA, 89/191 had cognitive impairment; for NIH-TB language, 138/196 had >25% and 58 had ≤25%; for NIH-TB working memory, 134/196 had >25% and 62/196 had ≤25%	Weak correlation between UPSIT and MoCA ($r = 0.30$, $p = 0.0002$); weak correlation between UPSIT and NIH-TB language ($r = 0.36$, $p < 0.0001$)
Damiano et al. (2023)	701, 334 females	55.3 ± 14.6, 95% CI: 54.3–56.3	Survey	MCS, MMSE, TMT, DSST, Neuropsychological Battery CERAD	9% had parosmia, 18% had moderate and severe olfactory deficits	MCS 5.2 ± 4.16, MMSE orientation 8.27 ± 3.25, TMT-A 65.5 ± 48.0, verbal fluency 15.57 ± 5.43, DSST 32.3 ± 19.3, Boston naming 13.15 ± 2.27, word list 15.35 ± 4.7, construction praxis 8.26 ± 2.55, word list recall 4.86 ± 2.25, word list recognition 7.88 ± 2.77	Parosmia significantly associated with MCS ($p = 0.001$) and Boston naming ($p = 0.017$); moderate & severe olfactory deficit associated with TMT-A ($p = 0.008$), digit-symbol ($p = 0.009$), word list memory task ($p = 0.041$)
Delgado-Alonso et al. (2022)	50, 37 females	51.06 ± 11.65	BSIT	Digit span (backwards), ROCF, Stroop A, inhibition test, determination test, divided attention, selective attention, FGT	9.00 ± 2.33	Frequency of impairment 2x more than expected for digit span, ROCF (memory at 30 min); frequency of impairment at least 3x more than expected for Stroop A; inhibition test 7.74 ± 3.91, determination test 198.31 ± 48.63, divided attention 561.37 ± 216.40, selective attention 429.66 ± 124.86, FGT Delayed Free Recognition I 5.70 ± 2.99	BSIT showed moderate correlations with digit span (backwards) ($R = 0.505$), ROCF (memory at 30 min) ($R = 0.383$), Stroop A ($R = 0.387$), inhibition test ($R = -0.374$), determination test ($R = 0.36$), divided attention ($R = 0.335$), selective attention ($R = -0.318$), and FGT (Delayed Free Recognition I) ($R = 0.347$)
Desai et al. (2022)	49, 36 female	18–76	Survey, UPSIT	CNS Vital Signs validated cognitive remote testing website, neurocognitive index, composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, simple attention, motor speed	Survey: *active COVID-19:* 13% had anosmia and 50% had hyposmia *recovered:* 4% had anosmia and 67% had hyposmia UPSIT: *active COVID-19:* 37.5% had anosmia, 18.75% had hyposmia, 43.75% had normosmia *recovered:* 33.33% had anosmia, 46.67%, had hyposmia, 20% had normosmia	Active vs. recovered cognitive flexibility 48.9 vs. 34.8, complex attention 46.6 vs. 49.0, composite memory 42.7 vs. 43.8 executive fxn 52.4 vs. 34.7, motor speed 49.1 vs. 43.2, neurocognitive index 47.1 vs. 35.8, processing speed 57.5 vs. 42.0; rxn time 49.0 vs. 31.0, simple attn. 46.4 vs. 49.8, verbal memory 43.1 vs. 45.9, visual memory 45.3 vs. 45.8	No correlation between self-reported smell loss and cognitive function; nonsignificant inverse association between UPSIT score and processing speed in recovered; no correlations with cognitive percentiles and UPSIT total scores

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TABLE 1 (Continued)

Authors, year	*n*, gender	Mean age±SD, range	Olfactory assessment methods	Cognition assessment methods	Olfactory results	Cognition results timepoint	Relationship between olfaction and cognition
Di Stadio et al. (2022)	152, 102 females	41.2 ± 11, 18–65	Sniffin' Sticks identification	MMSE, survey	50/152 had anosmia, 25/152 had hyposmia, 10/152 had parosmia/cacosmia, 58/152 had combination of hyposmia and parosmia	MMSE wnl; 23.7% reported mental clouding	Patients with mental clouding had higher risk of suffering from anosmia (OR 19, p = 0.05), hyposmia + parosmia (OR 33, p = 0.01), hyposmia alone (OR 15, $p = 0.07$), and moderate risk of suffering from parosmia (OR 3, $p = 0.5$) compared to patients with no neurological symptoms
Ferrucci et al. (2022)	$Time_1$: 76, 20 females; $Time_2$: 53, 15 females	56.24 ± 12.08, 18–75	Survey	BRB-NT, SRT, SPART, SDMT, PASAT, WLG	$Time_1$: 44.6% had hyposmia, 42.1% had hyposmia and dysgeusia $Time_2$: 9.4% had hyposmia	SPART-D = 5.66 ± 2.07, SRT-LTS = 35.64 ± 13.77, SRT-CLTR = 27.75 ± 13.06, SRT-D = 6.92 ± 2.66, SPART = 17.75 + 5.01, SDMT = 38.81 ± 9.88, PASAT-3 = 41.66 ± 11.98, PASAT2 = 30.81 ± 9.36, WLG = 24.75 ± 4.69	SPART-D (delayed visuospatial memory recall) score worse in those who reported hyposmia
Fiorentino et al. (2022)*	84, 55 females	42.8 ± 13.6, 19–59	Sniffin' Sticks, TODA	PPTT, generic naming test from Grémots battery: Evaluation du langage dans les pathologies neurodégénératives	Sniffin' Sticks: *age 19–39:* T 4.76 ± 4.04, D 9.51 ± 3.84, I 9.40 ± 3.92, TDI 23.68 ± 9.68 *age 40–59:* T 4.25 ± 3.26, D 9.55 ± 3.86, I 10.15 ± 3.52, TDI 23.95 ± 8.61 TODA *age 19–39:* threshold 1.66 ± 0.97, identification 3.97 ± 1.76 *age 40–59:* threshold 1.41 ± 0.87, identification 4.19 ± 1.63	Age 19–39: PPTT 47.31 ± 2.63; generative naming strict 34 ± 2, broad 34 ± 1, time 63.93 ± 17.51 age 40–59: PPTT 49.20; generative naming strict 34 ± 1, broad 35 ± 1, time 59.46 ± 16.34	For PPTT and TODA T, small significant correlation between semantic memory and odor threshold detection
Jennings et al. (2022)	108, 76 females	46.3 ± 10.3, 25–78	Survey	Survey	21/108 had dysosmia	71 had brain fog, 37 did not have brain fog	25.4% of participants with brain fog reported dysosmia, 8.1% of participants without brain fog reported dysosmia; in cluster analysis, dysosmia was more prevalent in the brain fog group in a two-cluster model
Kopishinskaia et al. (2021)	187, 152 females	35, 21–87	Survey	Survey	All patients had parosmia/phantosmia	40/187 had brain fog	Brain fog was significantly higher in patients with parosmia/phantosmia compared to controls

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TABLE 1 (Continued)

Authors, year	*n*, gender	Mean age±SD, range	Olfactory assessment methods	Cognition assessment methods	Olfactory results	Cognition results timepoint	Relationship between olfaction and cognition
Llana et al. (2022)*	42, 38 females	31–51	Survey	MTT, PAL, MoCA, DSST	17/42 had anosmia, 25/42 did not have anosmia	MTT ERI-d2: anosmics −9.01 ± 55.78, non-anosmics −49.81 ± 44.19; MoCA: anosmics 25.81 ± 2.42, non-anosmics 26.39 ± 2.64, controls 28.07 ± 1.58; DSS-M: anosmics 64.50 ± 16.08, controls 84.59 ± 10.64; DSS-IL anosmics 10.19 ± 4.79, controls 13.41 ± 3.71; DSS-R anosmics 6.81 ± 1.47, controls 7.83 ± 1.04	For MTT, ERI-d2 index was Higher in anosmics than non-anosmics with COVID-19; anosmics had lower scores on MoCA and DSST than controls without COVID-19
Tavares-Júnior et al. (2022)	141, 89 females	48 ± 14, 16–90	Survey	ACE-R, MMSE, CDR	Normal cognition: 19 had anosmia, 29 did not Cognitive impairment:1 had anosmia, 24 did not Subjective cognitive decline: 23 had anosmia, 45 did not	48 had normal cognition, 25 had cognitive impairment, 68 had subjective cognitive decline	Cognitive impairment group had a lower frequency of anosmia than the normal and subjective cognitive decline groups

*These studies contain only participants between ages 18 and 60.

ACE-R, Addenbrooke's cognitive examination-revised; BRB-NT, brief repeatable battery of neuropsychological tests; BVMT-R, brief visuospatial memory test-revised; CDR, clinical dementia rating; DSS-IL, digit symbol substation incidental learning; DSS-M, digit symbol substation correctly matched; DSS-R, digit symbol substation incidental learning registered; DSST, digit symbol substitution test; FGT, figural memory test; HVLT-R, Hopkins verbal learning test-revised; JLO, judgment line orientation test; MCS, memory complaint scale; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; MTT, mirror tracing test; MTT ERI-d2, mirror tracing test consolidation of learning; PAL, paired-associated learning; PASAT, paced serial additions test; PPTT, pyramids and palm trees test; RAVLT, Rey auditory verbal learning test; ROCF, Rey-Osterrieth complex figure; SDMT, symbol digit modality test; SPART, spatial recall test; SPCT, Salthouse perceptual comparison test; SRT, serial recall test; TMT, trail making test; WLG, word list generation.

normosmics and those with smell loss (Alemanno et al., 2021; Cacciatore et al., 2022; Caspersen et al., 2022). Seven studies found that those with smell loss had worse cognition than those without (Almeria et al., 2020; Kopishinskaia et al., 2021; Cecchetti et al., 2022; Ferrucci et al., 2022; Jennings et al., 2022; Llana et al., 2022; Damiano et al., 2023), and one study found that those with smell loss had better cognition (Tavares-Júnior et al., 2022). This discrepancy was resolved among results from studies that utilized a psychophysical assessment of olfaction. In these six studies, five reported significantly worse cognitive performance in the smell loss group (Azcue et al., 2022; Chen et al., 2022; Delgado-Alonso et al., 2022; Di Stadio et al., 2022; Fiorentino et al., 2022), with the remaining study reporting no significant difference (Desai et al., 2022).

3.4. Assessment of cognition

Methods for assessing cognition are widely heterogenous in these studies and consist of both self-report and clinical assessment. Some cognitive tests examine general cognition through screening tools such as the Montreal cognitive assessment (MoCA) or mini-mental state examination (MMSE), while other tests focus on specific cognitive domains. Assessment methods utilized in 3 or more studies include MoCA, MMSE, symbol digit modality test (SDMT), and generalized survey instruments.

There were no apparent patterns for certain cognitive tests to associate with significant findings, other than those including a factor to evaluate memory. Memory, including working, verbal, visual, and semantic memory, was specifically tested in nine of the studies. Of these, seven studies found that those with olfactory dysfunction had significantly worse memory than those without olfactory dysfunction (Azcue et al., 2022; Cecchetti et al., 2022; Chen et al., 2022; Delgado-Alonso et al., 2022; Ferrucci et al., 2022; Fiorentino et al., 2022; Damiano et al., 2023), while two studies found no significant difference (Caspersen et al., 2022; Desai et al., 2022).

As a caveat, 4/17 studies used a survey to assess patient cognition; two of these studies showed a significant relationship between olfaction and cognition, where olfaction was also only assessed with a self-report survey (Kopishinskaia et al., 2021; Jennings et al., 2022). The study by Caspersen et al. (2022) similarly utilized surveys to assess both cognition and olfaction, though this study did not find any significant associations between them. A single study (Di Stadio et al., 2022) used both survey and MMSE to assess cognition of participants and showed a significant relationship between survey outcomes (e.g., mental clouding) and olfactory dysfunction. However, the MMSE data for Di Stadio et al. (2022) showed that participants scored an average that was within normal limits.

3.5. Relationship between olfaction and cognition

Thirteen of the included studies demonstrated a significant association between olfaction and cognition, with all but one of these suggesting lower cognitive performance among those with olfactory dysfunction (Almeria et al., 2020; Kopishinskaia et al., 2021; Azcue et al., 2022; Cecchetti et al., 2022; Chen et al., 2022;

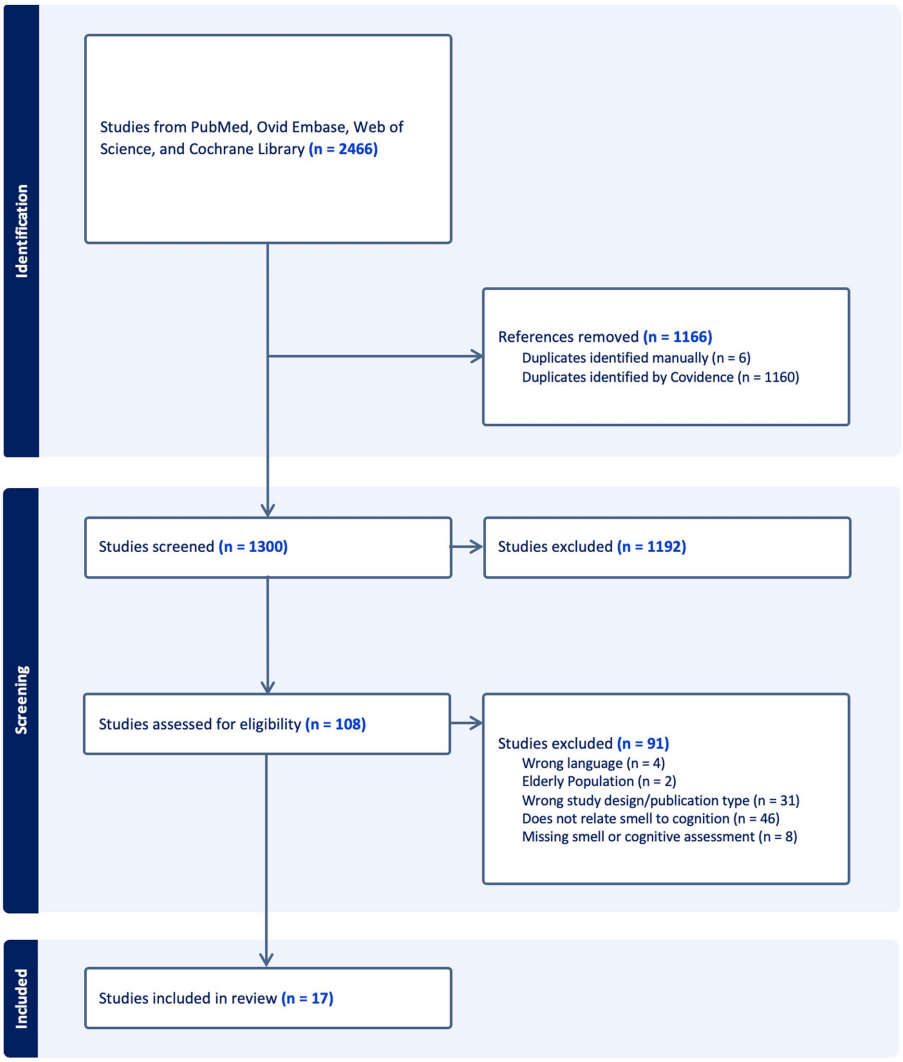

FIGURE 1
PRISMA-style flow chart documenting the study screening process.

Delgado-Alonso et al., 2022; Di Stadio et al., 2022; Ferrucci et al., 2022; Fiorentino et al., 2022; Jennings et al., 2022; Llana et al., 2022; Damiano et al., 2023). However, one study reported a lower frequency of anosmia in those with cognitive impairment compared to controls (Tavares-Júnior et al., 2022), and four studies found no statistically significant association between olfaction and cognition (Alemanno et al., 2021; Cacciatore et al., 2022; Caspersen et al., 2022; Desai et al., 2022).

3.6. Impact of severity of smell loss on cognition

Results from these studies are in-line with a dose-dependent relationship between the severity of olfactory dysfunction and neurocognitive deficits. Of the six studies that used psychophysical olfactory testing, which can detect varying levels of olfactory deficit severity, five found positive correlations between scores of olfaction and neurocognition. Azcue et al. (2022) and Delgado-Alonso et al. (2022) found statistically significant positive correlations between the BSIT and multiple tests of cognition. Chen et al. (2022) found a positive correlation between the UPSIT and the MoCA and NIH-TB tests. Fiorentino et al. (2022) used the TODA test of olfaction and PPTT test of cognition and found a positive correlation between odor detection threshold and semantic memory. The Di Stadio et al. (2022) study used the Sniffin' Sticks test to stratify olfactory deficit severity into categories of normosmia, hyposmia, and anosmia. Although all of the patients in that study scored in the normal range in the MMSE, patients who reported subjective mental clouding had a greater odds of anosmia (OR 19, $p = 0.05$) and hyposmia alone (OR 15, $p = 0.07$), though neither of these achieved statistical significance. In contrast to the other five studies using semi-objective olfactory assessments, Desai et al. (2022) found no apparent correlation between olfaction (assessed by UPSIT) and measures of cognition across patients actively infected with COVID-19 and those recovered from COVID-19. Interestingly, they found an inverse correlation between UPSIT scores and processing speed specifically in the COVID-19 recovered patients, though this relationship was not statistically significant ($p = 0.122$). However, unique to this study, the UPSIT test was self-administered rather than proctored.

4. Discussion

4.1. Summary of findings

A statistically significant association between olfactory deficits and poorer cognition was reported in 12 of 17 studies. Four studies found no association between olfaction and cognition. One study noted lower anosmia frequency in those with cognitive impairment. The methods used to assess olfaction and cognition were heterogenous and included both subjective self-reported measures and psychophysical clinical assessments.

4.2. Methods of olfactory assessment

Although patient report is the least time-consuming method for assessing olfactory status, it has been shown to consistently offer a less accurate measurement of olfaction (Philpott et al., 2006). Variability in reported associations between olfaction and cognition could thus reflect a decreased reliability of self-reported olfactory status. It is important to note that there are several components contributing to an individual's olfaction; namely, the presence of olfactory threshold, discrimination, and identification, where these complementary domains help to parse out specific pathways that contribute to the sense of smell (Hummel et al., 1997). Importantly, these domains localize to specific components of olfactory detection and processing. Olfactory threshold primarily represents the peripheral olfactory system whereas discrimination and identification may represent higher cognitive processing and, unlike olfactory threshold, are frequently unchanged in states of sinonasal disease (Hedner et al., 2010; Oleszkiewicz et al., 2019). All of the studies included in this scoping review used either survey, retrospective chart review, or olfactory identification testing to elucidate olfactory status among subjects, suggesting a need to evaluate individuals with persistent olfactory dysfunction following COVID using a more comprehensive examination of threshold, discrimination, and identification alongside cognitive testing to fully understand the impact of PASC on these domains.

4.3. Methods of cognitive assessment

Among studies that focused on assessment of memory as a cognitive domain, seven of nine identified worse outcomes in memory test results among those with olfactory dysfunction compared to those without. Interestingly, prior studies in patients with Alzheimer disease have demonstrated that impaired olfactory identification may predict an individual's memory decline (Zou et al., 2016; Yu et al., 2018). The relationship between olfactory dysfunction and diminished memory may be due to the role that one's sense of smell has on memory formation (Herz, 2016; Bruijn and Bender, 2018). In contrast, the use of self-reported cognitive assessments via survey produced more heterogeneous results when examining the relationships between olfaction and cognition. Even within the results of one study itself (Di Stadio et al., 2022), there were mixed results with the use of self-report versus objective measurements of cognition. This discrepancy in cognition between objective normalcy and subjective dysfunction highlights the difficulty of drawing conclusions from patient-reported data.

4.4. Parosmia and cognition

Qualitative smell loss (parosmia) appears to have a unique impact on patient cognitive domains in comparison to quantitative smell loss (hyposmia/anosmia). The study by Di Stadio et al. (2022) describes that parosmia has a small and statistically insignificant impact on subjective patient reports of mental clouding. At the same time, Damiano et al. (2023) found parosmia to have a significant association with post-COVID-19 patient scores on the Memory Complaint Scale (MCS), a subjective measure of one's perceived cognitive abilities. They also show that parosmia is significantly associated with objective neuropsychiatric morbidity via lower scores on the Boston Naming Test, an objective assessment of visual confrontation naming, language, communication, memory, and problem-solving processes. Interestingly, Di Stadio et al. (2022) found that patients with a combination of hyposmia and parosmia had the highest odds of reporting mental clouding. The disparate findings between these studies may indicate that the patients who report parosmia and are later found to be hyposmic on semi-objective olfactory assessment are at the greatest risk for measurable neuropsychiatric impairment. The disparate effects that parosmia and hyposmia/anosmia have on neurocognition could be explained by varying degrees of neuroinvasion, downregulation of olfactory receptors, or possibly due to an overlap of these phenomena leading those with semi-objectively assessed smell loss to have more robust cognitive changes than those with subjective smell loss alone (Yachou et al., 2020; Zazhytska et al., 2022).

4.5. Global relationship between olfaction and cognition

There are many studies which have examined the general relationship between olfaction and cognition with the majority showing that olfactory performance tends to have significant associations with measurements of frontal lobe executive function (Westervelt et al., 2005; Challakere Ramaswamy and Schofield, 2022; Mattos et al., 2022). There are a variety of medical conditions in which there is evidence for a positive association between olfactory performance and cognitive functioning. Some of the most robust findings for this correlation have been shown in neurodegenerative, multiple sclerosis, psychiatric, and traumatic brain injury (TBI) populations (Devanand et al., 2010; Challakere Ramaswamy and Schofield, 2022). Several of these conditions have a strong basis for concurrent disease mechanisms causing dysfunction in both cognition and olfaction. For example, TBI commonly affects the frontal lobe during rapid acceleration/deceleration head injury, which can lead to executive function deficits (Rabinowitz and Levin, 2014). Simultaneously, TBI can lead to olfactory dysfunction through sinonasal tract disruption, shearing of the olfactory nerve, or contusion of olfactory bulb and cortex (Howell et al., 2018). In the case of neurodegenerative disease, patients with Lewy bodies (e.g., Alzheimer's disease with predominantly limbic Lewy bodies) have diffuse proteinopathy that most commonly affects the olfactory bulb along with other brain regions leading to olfactory and cognitive impairment (Beach et al., 2009).

Unlike states of trauma or neurodegeneration, the mechanism linking olfactory dysfunction to cognitive deficits in a younger, healthy patient population is less understood. Recently, there have

been studies suggesting that humans have an intrinsic association between olfactory identification and spatial memory even outside of disease states (Dahmani et al., 2018). Given this association, a natural question is whether declines in olfactory function could independently contribute to cognitive deficits. A significant body of research early in the COVID-19 pandemic focused on the possibility of SARS-CoV-2's ability to directly invade the central nervous system through the olfactory mucosa and olfactory nerve (Kumari et al., 2021; Meinhardt et al., 2021). However, there is now substantial evidence indicating that these studies may have simply identified residual SARS-CoV-2 spike proteins within the brain without identifying the virus itself (Butowt et al., 2021). Additionally, there is now a strong model showing that early-stage SARS-CoV-2-induced anosmia stems from altering the function of olfactory sensory neurons rather than through direct infection (Zazhytska et al., 2022). Therefore, the growing evidence of COVID-related olfactory deficits without signs of direct neuroinvasion suggests that the mechanism linking post-COVID olfactory dysfunction with cognitive deficits could be related to the intrinsic association between olfaction and cognition in humans.

4.6. Limitations

This study is not without limitations. Out of the 17 studies, only three studies provided a population exclusive to individuals between 18 and 60 years of age. The remaining 14 studies included more heterogeneity in the age of their study populations and included participants who were older than 60 years. As individuals age, not only are they at higher risk for neurodegenerative diseases such as dementia, but also their cognitive functioning in certain areas such as processing speed and working memory may also decline (Harada et al., 2013; Murman, 2015). Additionally, there is a pronounced decrease in olfactory performance among people ages 60–71 years (Oleszkiewicz et al., 2019).

The studies included in this review each contained highly variable numbers of participants, where the disparate quantities of study participants add complexity when comparing the strength of findings between papers. For example, there are high-powered studies including several with 100+ participants that show disparate conclusions regarding correlations between olfaction and cognition. The Caspersen et al. (2022) study included 774 participants and found that there was no significant correlation between olfaction and cognition after COVID. At the same time, the Damiano et al. (2023) study included 701 participants and found there to be highly significant associations between olfaction dysfunction and worse cognitive performance in several cognitive tests. The disparities between these studies could be attributed to their varying methods for assessing both olfaction and cognition. Specifically, the use of subjective, survey-based assessments for olfaction (11/17 studies) and cognition (4/17 studies) limits the strength of objective conclusions on the relationship between these domains. Another limitation is the varying frequency of olfactory impairment among populations included, as some studies showed that nearly half of the participants exhibited olfactory dysfunction (Desai et al., 2022; Ferrucci et al., 2022), while others show that only ~20% of participants screened positive for olfactory dysfunction (Alemanno et al., 2021; Azcue et al., 2022; Cacciatore et al., 2022; Jennings et al., 2022). Additional studies utilizing psychophysical assessments of both olfaction and cognition along with larger numbers of participants with post-COVID olfactory dysfunction will help to better understand the effect COVID-19-related olfactory dysfunction has on cognitive performance.

5. Conclusion

The majority of studies in this review find that olfactory dysfunction is associated with poorer cognition, consistent with prior research in the area of neurodegenerative diseases, but a unique finding for post-infectious olfactory dysfunction. Despite these findings, studies that include individuals of highly variable ages fail to fully isolate the effects of aging on olfaction and cognition. Additional longitudinal, prospective studies are needed to understand how olfaction provides a window into the central nervous system in individuals affected by acute and chronic sequelae of COVID-19.

Author contributions

BV and PJ created and revised the search terms. BV, PJ, JT, and NW all served as independent reviewers for the title, abstract and full-text screening processes and wrote the article. DG, TG, DD, and JO conceptualized the topic and themes for this manuscript, provided direct supervision of the review process, and provided edits and revisions for the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A: Search Terms

PubMed (864 results)

((“Smell”[MeSH] OR “olfaction disorders”[MeSH] OR “Anosmia”[MeSH] OR smell [tiab] OR olfact*[tiab] OR phantosmia*[tiab] OR parosmia*[tiab] OR hyposmi*[tiab] OR anosmi*[tiab] OR cacosmi*[tiab] OR dysosmi*[tiab]) AND (“Cognitive dysfunction”[MeSH] OR “Cognition”[MeSH] OR cogniti*[tiab] OR “brain function*”[tiab] OR neurolog*[tiab] OR “mental status*”[tiab] OR memor*[tiab] OR “executive dysfunction*”[tiab]) AND (“COVID-19” [MeSH] OR “SARS-CoV-2” [MeSH] OR “Post-Acute COVID-19 Syndrome” [MeSH] OR COVID [tiab] OR “SARS-CoV-2”[tiab] OR nCoV [tiab]))

Ovid Embase (1,465 results)

((smelling/ or smelling disorder/ or anosmia/ or (smell or olfact* or phantosmia* or parosmia* or hyposmi* or anosmi* or cacosmi* or dysosmi*).tw.) and (cognitive defect/ or cognition/ or (cogniti* or brain function* or neurolog* or mental status* or memor* or executive dysfunction*).tw.) and (coronavirus disease 2019/or (COVID or “SARS-CoV-2” or nCoV).tw.))

Web of Science (Core Collection – Clarivate) (838 results)

TS = ((smell OR olfact* OR phantosmia* OR parosmia* OR hyposmi* OR anosmi* OR cacosmi* OR dysosmi*) AND (cogniti* OR brain function* OR neurolog* OR mental status* OR memor* OR executive dysfunction*) AND (COVID OR “SARS-CoV-2” OR nCoV))

Cochrane Library (71 results)

((smell OR olfact* OR phantosmia* OR parosmia* OR hyposmi* OR anosmi* OR cacosmi* OR dysosmi*) AND (cogniti* OR brain function* OR neurolog* OR mental status* OR memor* OR executive dysfunction*) AND (COVID OR “SARS-CoV-2” OR nCoV))

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Camera-based visual feedback learning aid for recovering sense of smell and taste in COVID-19 survivors: a proof-of-concept study

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Introduction: A significant proportion of people report persistent COVID-19-related anosmia, hyposmia or parosmia, often accompanied with ageusia, hypogeusia or dysgeusia. Here, we present a proof-of-concept study that assessed the feasibility and acceptability of a new Camera-Based Visual Feedback Learning Aid (CVFLA) and explored its potential to restore or improve persistent COVID-19-related smell and/or taste impairment.

Methods: Fifteen adult participants with persistent smell and/or taste impairment were randomly allocated to 7-, 14-, or 21-days baseline of symptom monitoring before receiving the intervention in up to 10 sessions (length and frequency determined by participant's preference and progress) using a specialised CVFLA apparatus (patent no. 10186160). Smell and taste were assessed pre- and post-intervention subjectively, and also objectively using the ODOFIN Taste Strips and Sniffin Sticks. Participant feedback about their experience of receiving CVFLA was obtained via a semi-structured interview conducted by someone not involved in delivering the intervention.

Results: The intervention was extremely well received, with no dropouts related to the intervention. There was also a significant improvement in smell and taste from pre- to post-CVFLA intervention (mean number of sessions = 7.46, *SD* = 2.55; total duration = 389.96 min, *SD* = 150.93) both in subjective and objective measures. All participants, except one, reported experiencing some improvement from the 2nd or 3rd session.

Discussion: This new CVFLA intervention shows promise in improving COVID-19 related impairment in smell and taste with a very high level of acceptability. Further studies with larger samples are required to confirm its potential in restoring, improving or correcting smell and/or taste impairment in relevant clinical and non-clinical groups.

KEYWORDS

visual feedback, learning, smell, taste, COVID-19, impairment, intervention

1. Introduction

A new onset of smell or taste loss has been considered a clinical indicator of SARS-CoV-2 infection since the start of the pandemic (e.g., Borsetto et al., 2020; Costa and Carnauba, 2020; Giacomelli et al., 2020; Lechien et al., 2020; Spinato et al., 2020). About 1 in 5 people with COVID-19 report persistent (i.e., lasting more than 10 days) COVID-19-related anosmia (loss

of the sense of smell), hyposmia (reduced sense of smell) or parosmia (distorted sense of smell; e.g., Chary et al., 2020; Chiesa-Estomba et al., 2020; Antolín-Amérigo et al., 2021; Printza et al., 2021). A similar proportion of people with COVID-19 report ageusia (loss of the sense of taste), hypogeusia (reduced sense of taste) or dysgeusia (altered perception of taste), with many people reporting both smell and taste impairment (Wang et al., 2023). Even though the prevalence of COVID-19-associated smell and taste impairment decreased with later variants of the virus (Boscolo-Rizzo et al., 2022), it still appears significant for the Omicron variant at around 12% in people with European ancestry (von Bartheld and Wang, 2023). Furthermore, persistent qualitative disturbances of smell and/or taste have been reported in around one-third of patients who recover from COVID-19 (Ercoli et al., 2021).

An early longitudinal study (Boscolo-Rizzo et al., 2022) that followed up people with COVID-19 for eight weeks found that one in three people had smell or taste impairment at four weeks, and 1 in 5 still had smell and/or taste impairment when assessed at eight weeks, with that the loss of smell and taste being the most prevalent long-lasting symptom, followed by fatigue and breathing problems. Later studies (e.g., Jensen et al., 2022) also show impaired smell in about 20% of people at six-months post-COVID 19. Full recovery of smell and/or taste may occur by one year in about half of such cases (Nguyen et al., 2021; review, Peterson et al., 2021; Boscolo-Rizzo et al., 2023) but may still persist in a significant proportion even two years after the infection (Boscolo-Rizzo et al., 2023).

Impaired sense of smell and taste have implications for mood and daily activities of the affected individuals. Empirical evidence shows that pleasant and unpleasant smells are powerful manipulators of mood and emotions (e.g., Kaviani et al., 1998) and, perhaps not surprisingly, smell and/or taste impairment in the context of COVID-19 has been associated with low mood and anxiety (Dudine et al., 2021), unhealthy eating patterns (Javed et al., 2022), reduced quality of life and safety related issues (Coelho et al., 2021) as well as with brain fog (Garcia-Melendez et al., 2023). Even in non-COVID populations, impaired sense of smell is reported to occur in people with depression (Pause et al., 2001, 2005; Pollatos et al., 2007; Yuan and Slotnick, 2014) and has been linked with cognitive impairment and depression in the elderly, in certain types of dementias (Suzuki et al., 2004; Seo et al., 2009) and known to influence appetite and immunity (Schiffman and Graham, 2000). Thus, there is a need to find acceptable and scalable interventions that can aid recovering of smell and taste in the context of COVID-19 as well as in other disabling conditions that commonly present with impaired sense of smell and/or taste.

The present study was designed to assess the acceptability, feasibility and potential benefits of a specialized Camera-Based Visual Feedback Learning Aid (CVFLA) in restoring, improving and/or correcting the sense of smell and taste, along with possible changes in mental health and well-being, in people with persistent COVID-19-related smell and/or taste impairment. This CVFLA involves the use of a camera-based technology and a specialized collar technique for smell and taste training whereby real time video feedback about the individual is observed, while the direct view of the self is obscured (patent no. 10186160). During a session, the individual "learns" by observing their self through real time video feedback. In an early study by Ramachandran and Rogers-Ramachandran (1996), a series of patients were reported to recover phantom limb sensation using a technique involving a virtual reality mirror box (a mirror placed vertically on the table and reflected the patients' intact hand superimposed on the experienced position of the phantom limb). There is recent evidence that visual feedback training can help to restore accurate sensation of the self, change sensations within the self (from discomfort to comfort and *vice-versa* as required), improve mobility, balance and movement, reduce pain, retrain stress responses, improve breathing, and many other sensations and pertaining to the individual (e.g., Deconinck et al., 2015; Kim and Lee, 2020; Pak and Lee, 2020). The specialized CVFLA we report had shown promise in unpublished case studies. The present proof-of-concept study aimed to examine the feasibility of delivering this intervention, its acceptability and potential to facilitate recovery of smell and taste that was lost or distorted due to COVID-19.

2. Methods

2.1. Participants

The study initially involved 16 adults residing in different parts of the UK who self-reported experiencing persistent COVID-19-related loss of smell and/or taste. Of these, 15 participants (5 males, 10 females; age range: 20–62 years) completed the study (one person could not continue for personal reasons). The participants were recruited through social media and contacts with relevant charities as well as from our ongoing COVID-19-related projects (Vakani et al., 2023). The study inclusion criteria required all participants to be (i) aged ≥18 years, (ii) experiencing persistent (lasting >10 days) smell and taste impairment following COVID-19 infection, and (iii) able to provide written informed consent.

The study was approved by the University Research Ethics Committee (ref no. 18771-LR-Oct/2019–20,701-1). All participants provided written informed consent and were compensated for their time and travel expenses. All study procedures followed ethical standards set by the Helsinki declaration (1964).

2.2. Design and procedure

The study utilized a non-concurrent multiple baseline across participants design (Watson and Workman, 1981). This is a type of single-case design where each participant acts as their own control, and can be used to study the effect of an intervention across several participants. When using this design, the intervention for any given problem or behavior begins at different times for the different participants; and effects of the intervention are shown when changes in the target problem/behavior are observed that coincide with the intervention and do not systematically covary with the duration of the baseline. For this study, we opted for a non-concurrent type to allow more flexibility in recruiting participants, especially when the pandemic-related restrictions in the context of laboratory-based research studies at the university were continuously changing. The study involved three different pre-selected baselines (7 days, 14 days, and 21 days), with an equal number of participants in a pre-determined sequence allocated to each of the three baselines to avoid experimenter bias (Christ, 2007).

Of 15 participants in the study, five participants had been allocated to receive the CVFLA intervention after 7 days, five participants after

14 days, and five participants after 21 days of baseline periods of monitoring for changes in the sense of smell and/or taste (see Table 1). However, one of the participants who had been allocated to start receiving the intervention after a 14-day baseline, started receiving the intervention a week later than planned due to personal reasons, and hence a 14-day baseline became a 21-day baseline in this case. Therefore, there were only four participants with a 14-day baseline monitoring and six participants with a 21-day baseline period in the final sample; this, if anything, contributes to the robustness of the results as a 21-day baseline was sufficiently long for smell and taste to return (but it did not happen) spontaneously without the CVFLA intervention.

Prior to being allocated to 7/14/21 days of baseline (smell and taste monitoring), all participants were carefully screened to ensure they met our study inclusion criteria (see Table 1). In addition, information was obtained for any known allergies and medical history. The selected participants were asked to subjectively rate their sense of smell and taste during their allocated baseline period, and invited for the pre-intervention assessments if their smell and taste impairment persisted at the end of the allocated baseline period (found to persist in all cases) (Table 1).

For pre-intervention assessments, a trained researcher (SC or KV) administered a range of self-report measures to obtain information on participants' COVID history, mental health and well-being, interoceptive awareness, smell and taste impairment, and objectively assessed their smell and taste impairment using an ODOFIN taste strip and Sniffin stick test kit (Rumeau et al., 2016). They then received the intervention (see "CVFLA Intervention" CVFLA intervention) and were re-assessed one week after the last intervention session on the same measures as used for pre-intervention assessments. All 15 participants provided subjective ratings of smell and taste impairment after the last intervention session (audio-video recordings obtained and the videos subsequently rated by someone who was not involved in delivering the intervention for scoring purposes), but four (three with significant travel commitments, and one re-infected with COVID-19) of the 15 participants did not complete the remaining post-intervention assessments.

2.3. Pre- and post-intervention assessments

Smell and taste, mental health and well-being, and interoceptive awareness were assessed before and after the intervention. In addition, a semi-structured interview was conducted at the very end of study participation (post-intervention) by a researcher who was not involved in delivering the intervention (KV) to gather participant feedback about the acceptability of the current version of the CVFLA and possible future improvements.

2.3.1. Smell and taste

Smell and taste impairments were first assessed subjectively by asking the participants to rate their ability to smell (loss of smell and distorted sense of smell) and taste (loss of taste and distorted sense of taste) on a seven-point scale ["not at all" (0) to "very severe" (6)]. The ODOFIN *Taste and Sniffin Sticks* (Rumeau et al., 2016) were then used to measure smell and taste impairment objectively. The ODOFIN smell and taste identification test has 12 Sniffin sticks of different odors (orange oil, leather, cinnamaldehyde, peppermint oil, banana, lemon oil, anethole, coffee, clove oil, pineapple, rose, and fish) and four paper strips impregnated with salt, sugar, sour, and bitter taste. Each stick was presented with a gap of 5 s under three conditions (smelling with left, right, and both nostrils respectively). Each time, a cue card was presented with four options to sniff the stick and choose the option that matched their olfactory perception. They were asked to guess the smell if they could not smell anything. A total score was achieved for each condition by adding the individual response, with 0 indicating "no smell" and 12 indicating "maximum ability to smell". Four taste strips were given with a gap of 30 s, and a cue card was presented with four different options. They were asked to choose the option that matched their taste perception. A score of 0 was given if the response was wrong, and a score of 1 was given if it was correct. All information, including prompted/unprompted answers, whether guessed, known, or remembered from the previous trial, distorted or no smell/taste, were recorded on a separate scoring sheet.

2.3.2. Mental health and well-being

The levels of depression, anxiety and stress were assessed using the Depression Anxiety and Stress Scale (DASS-21; Lovibond and Lovibond, 1995). This 21-item self-report scale has three subscales (each with seven items): depression, anxiety and stress. Each item is rated on a four-point scale (0 to 3) based on how often in the past week it applied to them. Higher scores indicate higher levels (severity) of symptoms. Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest, anhedonia, and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect.

TABLE 1 Study design and phases.

Screening	Baseline	Pre-intervention Assessments	CVFLA Intervention	Post-intervention Assessments
1. Demographics 2. COVID history 3. Smell and Taste impairment 4. *If found to meet inclusion criteria – allocated to* 7, 14, or 21 days of smell and taste monitoring	7, 14, or 21 days of symptom (smell and taste) monitoring *If smell and taste impairment still present (self-reported) at the end of the allocated baseline period – invited for Pre-intervention Assessment*	1) Smell and Taste 2) Mental health and well-being 3) Interoceptive awareness	Up to 10 sessions over 5–10 weeks	1) Smell and Taste 2) Mental health and well-being 3) Interoceptive awareness 4) Semi-structured interview to obtain participant feedback about their experience of the CVFLA

Finally, the stress scale assesses difficulty relaxing, nervous arousal, easily upset, agitated, irritable, over-reactive, and impatient.

Overall quality of life was assessed using the five-item World Health Organization Well-being Index (WHO-5, Bech et al., 1996). Participants rate each item on a six-point Likert scale based on their feelings over the past two weeks. Higher scores indicate a higher quality of life or level of well-being.

2.3.3. Interoceptive awareness

The Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2; Mehling et al., 2018) was used to assess interoceptive bodily awareness. It has 37 items, belonging to one of the eight dimensions: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trust. Each item is rated on a six-point scale ["never" (0) to "always" (5)], with higher scores indicating greater bodily awareness. The main reason for including this scale was to explore whether those scoring higher on this scale may benefit more from the CVFLA intervention; or whether the CVFLA intervention increases interoceptive awareness.

2.4. CVFLA intervention

The intervention was delivered by a researcher (SC) following a predetermined protocol in up to 10 sessions over 5–10 weeks, depending on the participant's progress and preference, with each session lasting up to 60 min. Typically, sessions 1–3 focused on introducing and implementing the CVFLA techniques, sessions 4–6 aimed to consolidate previous learning, and sessions 7–9 focused on confirming the re-learning of smell and taste.

All CVFLA sessions were conducted with participants sitting on a comfortable chair. During the first CLFLA session, the participant was briefed about the CVFLA set up (Figure 1) with a practical demonstration. A collar was then placed around their neck, and they were asked to observe themselves in real time (with ~100-ms delay) on the computer screen from two different views: (i) a close-up view to help them focus on the task that they were performing (e.g., smelling or tasting a food item) and (ii) a wide-angle view which showed a broader view of themselves sitting on the chair (Figure 1). If they reported feeling aroused or stressed (or appeared stressed), the demonstration was immediately paused, the collar was removed, the cameras were moved away, and a relaxation exercise (breathing and/or muscle relaxation) was introduced to give them time to recover. Once the participants were comfortable with the practical demonstration and the collar, the session began.

Before each session, the participants were asked to indicate their ability to smell and taste on a scale of 0 to 10, with zero indicating "no smell or taste" and 10 indicating "maximum smell or taste". This was followed by a breathing and muscle relaxation exercise. Specific smell and taste experiences for any particular food item were then generated in three successive attempts, with each attempt lasting for about 15–25 s. If the participant showed a clear improvement in smell or taste, further attempts were made with another food item in the same category; if no improvement occurred, a different item from a different taste category was presented. Within five taste categories (sweet, sour, salty, umami, and bitter), different food items (e.g., salt, jam, dates, cream crackers, malted biscuits, watercress) were presented; and within each category, the items were clustered by intensity, going from the least to the most intense within the session (e.g., umami - seaweed, soy sauce, bovril, marmite; sour- goji berries, cherries, cranberries; bitter- broccoli, rocket, kale, coffee beans). For the sour category, flavored and plain yoghurt, citrus fruits (grapes, raspberry, satsumas, oranges), apple cider vinegar, candies, lemon, and lime were given depending upon individual's progress. The food items were presented in a different order for individual sessions and participants depending upon the progress and choice of the participant. However, we consistently started all sessions with a tiny amount of sugar for all participants, regardless of the stage of intervention and progress of the individual, to maintain some consistency. The participants were not blinded to any food item and had been asked in advance for any known allergies and food/smell preferences. Whenever participants reported an unpleasant response (e.g., disgust or stress) to any food items, relaxation exercises were re-introduced to reduce their emotional stress response and/or physical tension. All sessions ended with a breathing or muscle relaxation exercise, as per the participant's preference.

In addition, during the second and subsequent CVFLA sessions, the participant was also asked to describe any observable changes (from the previous session) in their smell and taste (in addition to indicating their ability to smell and taste on a scale of 0 to 10 as mentioned above for all sessions). These sessions proceeded with taste/flavors based on the participant's experience from the previous session/week and their comments from the current week, focusing on food and smell items that still needed to be accurately tasted. The number of actual sessions depended upon the individual's progress. Throughout the sessions, participants' responses were recorded for identification accuracy and pleasantness/unpleasantness of the item.

2.5. Data analysis

As this was a proof-of-concept study with only 15 participants, the data for each participant on all key measures are first presented and summarized descriptively and then analyzed across the entire sample using repeated-measures analysis of variance (ANOVA) to explore the impact of the CVFLA on the primary outcome variable/s (i.e., improvement in the sense of smell and/or taste); the effect sizes where reported are partial eta squared (η_p^2; the proportion of variance associated with a factor). Next, Pearson's correlations were used to examine whether the pre- to post-CVFLA changes seen in the primary outcome variables were correlated with any baseline sample characteristics, including age, the duration of smell and taste impairment, various measures of mental health and well-being, and interoceptive awareness. Following the observation of significant associations of post-intervention reduction (improvement) in smell and taste impairment with age, the duration of smell or taste impairment, and the "Noticing" subscale of the MAIA-2 (Interoceptive Awareness), a stepwise regression analysis was run to explore the most robust correlate of the CVFLA-led improvement. Various measures of mental health and well-being, and interoceptive awareness, were also explored for any pre- to post-intervention changes using repeated-measures ANOVAs. Prior to running these analyses, the data properties (skewness, kurtosis) of all variables, including the subjective ratings of smell and taste, were examined and found suitable for parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

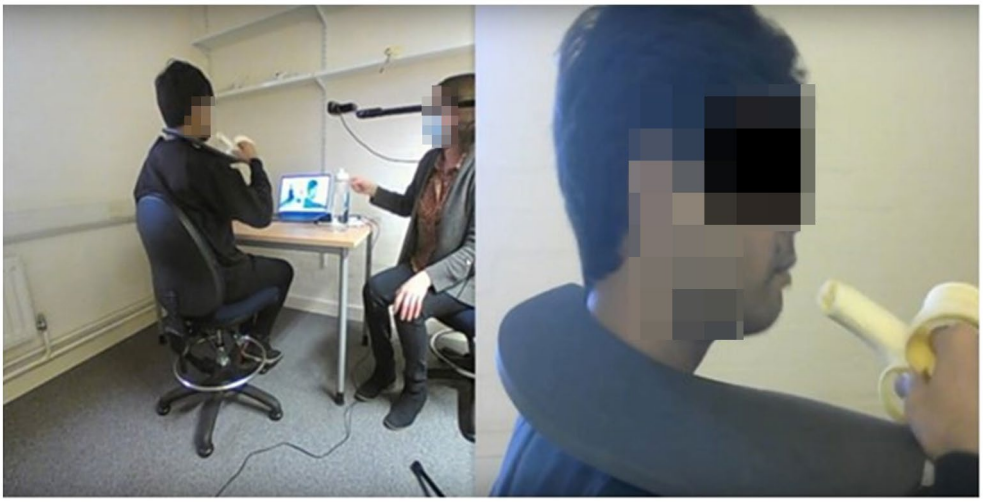

FIGURE 1
An illustration of the CVLFA set-up and intervention. This image is a screen shot from the computer screen that the participant is watching. The participant observes a real-time video of their actions, via the two webcams being streamed to the computer. The black collar, worn around the neck, blocks the individual's direct view of their self, meaning the visual information about their actions is now restricted to being **only** what they can see on the computer screen. In this illustration, as the banana is eaten, the taste of the banana may be re-learnt since the "taste" of the banana has been learnt previously, and most likely being predicted. The real-time video stream on the computer provides new/additional visual feedback for the participant to learn from.

All analyses were conducted using the Statistical Package for Social Sciences (for Windows, version 28; IBM, New York, United States).

3. Results

3.1. Sample characteristics

On average, the sample had moderate-to-severe smell and taste impairment, lasting for about 8 months prior to taking part in this study (see Tables 2, 3). None of the included participants had a neurodegenerative disorder, but one participant had rhinitis (no. 5), and one participant (no. 6) had asthma.

TABLE 2 Sample characteristics.

Sample characteristics	Mean (*SD*)	Range
Age (in years)	43.53 (12.25)	20–62
Duration of smell/taste impairment prior to receiving CVFLA (in days)	236.66 (234.91)	28–817
Mental health and well-being		
Depression (DASS-21)	9.13 (7.97)	0–30
Anxiety (DASS-21)	10.80 (10.25)	0–32
Stress (DASS-21)	13.33 (9.96)	0–30
Well-being Index 9 (WHO-5)	13.00 (4.31)	7–21
Introspective awareness		
Noticing (MAIA-2)	3.75 (0.86)	1.75–5
Not-distracting ((MAIA-2)	2.14 (1.39)	1.60–4.85
Not-worrying (MAIA-2)	2.87 (0.68)	0.60–3.80
Attention-regulation (MAIA-2)	3.15 (1.24)	1.29–5
Emotional- awareness (MAIA-2)	4.03 (0.81)	2.20–5
Self-regulation (MAIA-2)	3.38 (1.08)	1.50–5
Body-listening (MAIA-2)	2.75 (1.32)	1–5
Trusting (MAIA-2)	3.53 (1.23)	1–5

DASS-21, Depression Anxiety Stress Scale (DASS-21; Lovibond and Lovibond, 1995); WHO-5, World Health Organization Well-being Index (WHO-5; Bech et al., 1996). MAIA-2: Multidimensional Awareness of Introspective Awareness-2 (MAIA-2; Mehling et al., 2018)

3.2. CVFLA intervention delivery and acceptability

On average, study participants attended about seven intervention sessions (mean = 7.47; SD = 2.56), taking on average about 7 h per person (mean = 389.96 min, SD = 150.93). The intervention was extremely well received, as evident from responses to the feedback interview questions presented in Table 4. All participants found the intervention training to be "generally" or "definitely" useful and enjoyable and believed that it helped them to recover their sense of taste and/or smell. Around one-third (36.37%) of the sample reported that they had practiced the methods and techniques learnt during the sessions outside the sessions (e.g., at home), and they all stated that they would recommend this intervention to other individuals with taste and smell impairment. One person reported concerns regarding body image issues once they began to enjoy food after the fourth CVFLA session. Several participants reported during the last interview that they were skeptical about the intervention and found watching them on camera somewhat uncomfortable initially but were pleasantly surprised with how it helped them to recover their smell and taste. There were no drop-outs due to the CVFLA intervention not being acceptable.

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TABLE 3 Duration of smell and taste impairment, and subjective ratings of impairment before and after CVFLA for individual participants.

Participant No.	Age (years)	Sex	Duration of smell/taste impairment prior to receiving CVFLA (in days)	Baseline (in days)	Subjective ratings of impairment [scale 0 (none)-to-6 (very severe)]								Pre- to post-CVFLA decrease in impairment across smell and taste (total pre- *minus* total post ratings)
					Smell				Taste				
					Loss		Distortion		Loss		Distortion		
					Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	31	Female	172*	7	5	2	5	2	5	2	5	2	12
2	36	Female	28	14	5	0	0	0	5	0	0	0	10
3	49	Female	177*	21	4	2	4	3	4	3	4	3	5
4	50	Male	208	7	5	3	5	5	5	1	5	5	6
5	38	Female	207*	14	2	1	5	1	0	0	4	1	8
6	37	Female	207*	21	3	0	3	1	4	0	4	1	12
7	39	Female	50	7	6	0	6	3	5	0	5	2	17
8	59	Female	220*	14	6	2	6	1	1	1	1	1	9
9	60	Male	817*	21	4	2	2	1	1	2	0	1	1
10	41	Male	32	7	4	0	0	0	0	0	6	0	10
11	62	Female	533*	14	5	3	5	3	5	3	2	2	6
12	37	Female	619*	21	2	0	2	0	2	0	2	0	8
13	20	Male	54	7	5	3	5	3	2	1	3	1	7
14	36	Female	172*	21	5	1	5	1	5	1	5	1	16
15	58	Male	54	21	4	1	1	1	4	1	1	1	6

*Participants with impairment for more than 24 weeks.

3.3. Pre- to post-intervention changes in smell and taste impairment

In post-intervention subjective ratings, relative to the pre-intervention ratings, all participants reported less severe impairment (or no loss) in their sense of smell, 11 participants (of 13 participants with a distorted sense of smell at pre-intervention) reported less severe or no distortion of smell, 11 participants (of 13 participants who had taste impairment) showed a reduction in the severity of taste impairment, and 11 (of 13 participants) showed a less distorted sense of taste (Table 3). All participants, except one, started to report experiencing a positive change in smell and/or taste from the second or third session (session-wise data not presented as the number of sessions varied for individual participants depending on their progress); and each of the 15 participants showed some reduction in total (smell and taste) impairment as assessed by subjective ratings (see Figure 2).

When explored across the entire sample using repeated-measures ANOVAs, there was a significant reduction in subjective ratings of both smell and taste impairment after, compared to before, the CVFLA intervention (all $p \leq 0.004$), with somewhat larger effect sizes for smell than taste, and for recovery (based on "loss of smell" or "loss of taste ratings") relative to correction of distorted smell or taste (Table 5). This improvement (total across smell and taste loss and distortion ratings) was correlated negatively with age [$r = -0.514$ (95% CI −0.812, −0.023), $p = 0.05$] and the duration of smell or taste impairment [$r = -0.529$ (95% CI −0.819, −0.002), $p = 0.04$] and positively with pre-intervention scores on the "Noticing" dimension of the MAIA-2 (Interoceptive Awareness) scale [$r = 0.544$ (95% CI 0.043, 0.826), $p = 0.036$]; there was also a trend-level positive association with the Emotional-Awareness dimension of MAIA-2 [$r = 0.47$ (95% CI −0.055, 0.792), $p = 0.07$]. The regression model with these variables as predictors and improvement in smell and taste as the dependent variable was significant ($F = 5.45$, $df = 1, 14$, $p = 0.036$), with a significant effect of the 'Noticing' dimension (standardized coefficient $\beta = 0.544$, $t = 2.335$, $p = 0.036$); age, the duration of smell or taste impairment, and Emotional-Awareness (MAIA-2) were not significant (all $p > 0.10$). No measure of mental health, well-being, or interoceptive awareness showed a significant difference between pre- and post-CVFLA assessments (all p values >0.10).

An improvement in taste and smell following the intervention was also visible in the smell and taste identification accuracy (ODOFIN test) scores (Figures 3, 4) of 8 participants for whom pre- and post-intervention data were available (unavailable for 7 participants due to late arrival of the test kit or no final in-person follow-up assessment). Exploratory analyses of these data across the entire sample using repeated-measures ANOVAs (Table 5) indicated significantly higher identification accuracy for smells at the post-intervention assessment compared to the pre-intervention assessment ($p \leq 0.004$) (see Table 5). There was a positive change also for taste identification accuracy, but only at the trend level. Improvements in smell identification correlated in the same direction as noted earlier for subjective ratings but

TABLE 4 Post-CVFLA feedback from individual study participants.

Post-CVFLA Feedback (n-11)	Questions				
	Overall, how did you find the CVFLA?	Do you believe the CVFLA has aided in improving your loss and/or distorted sense of taste and/or smell?	Did you find the intervention enjoyable and helpful?	Did you practice the methods and techniques used during the sessions at home or any other place than the lab?	Will you recommend this to other individuals with Taste and Smell impairments?
	Response Options				
	1=not at all useful	1=not at all	1=not at all	1=not at all	1=not at all
	2=not really useful	2=not really	2=not really	2=not really	2=not really
	3=yes generally useful	3=yes generally	3=yes generally	3=yes generally	3=yes generally
	4=yes definitely useful	4=yes definitely	4=yes definitely	4=yes definitely	4=yes definitely
Participant no.	Participant responses				
01	4	4	4	1	4
03	3	4	4	1	4
04	4	4	4	4	4
05	3	3	4	1	4
09	4	4	4	2	4
10	3	4	3	4	4
11	4	4	4	4	4
12	4	4	4	4	4
13	3	4	4	2	4
14	4	4	4	2	4
15	4	4	4	2	4

non-significantly ($n = 8$) with symptom duration [$r = -0.688$ (95% CI -0.938, 0.032), $p = 0.059$] and Noticing dimension of the MAIA-2 (Interoceptive Awareness) scale [$r = 0.504$ (95% CI 0.311, 0.892), $p = 0.203$] (no correlation with age, $r = 0.016$).

4. Discussion

This was the first study to assess the feasibility and acceptability of a new Camera-Based Visual Feedback Learning Aid (CVFLA) and explore its potential to restore or improve persistent COVID-19-related smell and/or taste impairment. The findings demonstrated that this non-invasive intervention is highly acceptable and can be easily administered even in non-clinical settings, contributing to the accessibility and feasibility of the intervention. The findings also suggested that the intervention could be helpful to people who have COVID-19-related loss or distortion of smell and taste, with relatively stronger benefits in people who scored relatively higher on the "noticing" aspect of interoceptive awareness (assessed with items, such as "I notice changes in my breathing, such as whether it slows down or speeds up."). The effects of CVFLA seemed somewhat stronger for smell than taste; and for recovery of the lost smell or taste, relative to correction of distorted smell or taste though this might, at least partly, be explained by the sample characteristics (i.e., relatively more severe impairment of smell than taste; and relatively more participants with loss of the sense of smell/taste rather than the distorted sense of smell or taste).

The findings of this proof-of-concept study support the CVFLA as a novel and innovative approach to improving smell and taste that is scalable and may also be preferable to other treatments for taste and smell recovery, such as corticosteroids (Harless and Liang, 2016), which may cause dependency and side-effects in at least a proportion of the users. Furthermore, this approach to improving or correcting smell and taste may also be applied in many different clinical and non-clinical settings, for example, in the context of aging (Delgado-Lima et al., 2023) and neurodegenerative disorders (Hawkes, 2006) where smell and taste alterations are typical problems. However, this was the first study to have tested this intervention in a relatively small number of participants who appeared highly motivated to regain their sense of smell and taste (some people cried with happiness when first reporting improvement during the session). Further studies involving larger samples and appropriate control groups are needed to confirm

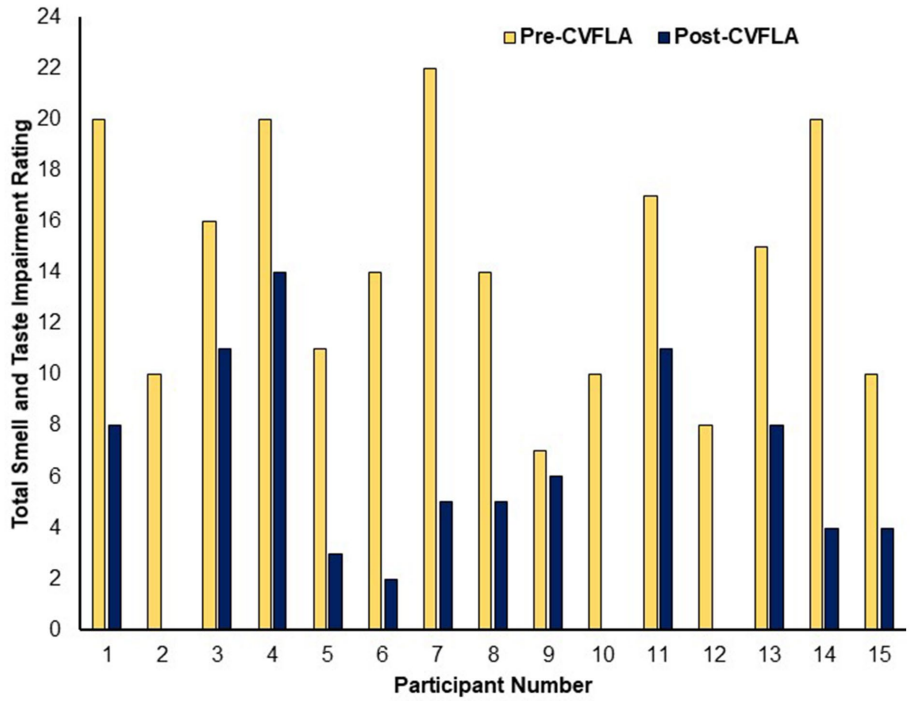

FIGURE 2
Subjective ratings of total smell and taste impairment before and after the CVFLA intervention.

TABLE 5 Descriptive statistics for subjective ratings of smell and taste impairment and objective (ODOFIN test) assessment of smell and taste identification accuracy before and after the CVFLA intervention and the results of the ANOVAs analyses.

Assessment	Pre-CVFLA (baseline)	Post-CVFLA	ANOVA: Pre- vs. Post-CVFLA comparison		
Subjective ratings of impairment	Mean (*SD*)	Mean (*SD*)	*F (df= 1.14)*	*p*	Effect size (η_p^2)
Loss of smell	4.33 (1.23)	1.33 (1.17)	72.69	**<0.001**	0.839
Distorted smell	3.60 (2.10)	1.67 (1.45)	21.25	**<0.001**	0.603
Loss of taste	3.20 (1.97)	1.00 (1.07)	18.68	**<0.001**	0.572
Distorted taste	3.13 (1.99)	1.40 (1.30)	11.92	**0.004**	0.460
Total (Smell and Taste) Impairment	14.27 (4.83)	5.40 (4.30)	67.19	**<0.001**	0.828
ODOFIN test for smell and taste identification accuracy[a]	Mean (*SD*)	Mean (*SD*)	*F* (*df* = 1.7)	*p*	Effect size (η_p^2)
Left nostrils	7.12 (2.36)	10.37 (1.40)	23.20	**0.002**	0.768
Right nostrils	7.37 (2.26)	10.37 (1.19)	12.60	**0.009**	0.643
Both nostrils	7.37 (2.39)	10.75 (1.03)	20.01	**0.003**	0.741
Taste test total[a]	3.12 (0.99)	3.87 (0.35)	4.20	0.08	0.375

[a]Sample size reduced to 8 due to late arrival of the test kit or missed final in-person follow-up assessment.

its potential for recovering or correcting smell and taste in relevant clinical and non-clinical populations.

Concerning the possible mechanisms that might be involved in smell or taste improvement following the CVFLA intervention, one possibility is that it facilitated re-learning of the smell or taste via their correct prediction by the brain (from previous episodic memories of the smell and food items) in response to the visual signals received during the intervention sessions (Clark, 2013; Hutchinson and Barrett, 2019). For example, as shown in Figure 1, the taste of a banana may be re-learnt with additional visual feedback provided to the participant to learn from, since the "taste" of the banana has been learnt previously and is most likely being predicted. Our finding showing a positive relationship between the 'noticing' aspect of interoceptive awareness and the degree of improvement suggests that attention and interoceptive awareness may facilitate this effect. There is recent evidence for COVID-19 related anosmia to be associated with higher functional connectivity between the left orbitofrontal cortex and visual association areas, along with greater cerebral blood flow in the hippocampus, insula, and posterior cingulate (Wingrove et al., 2023). Some of these areas may be involved in CVFLA-led benefits given

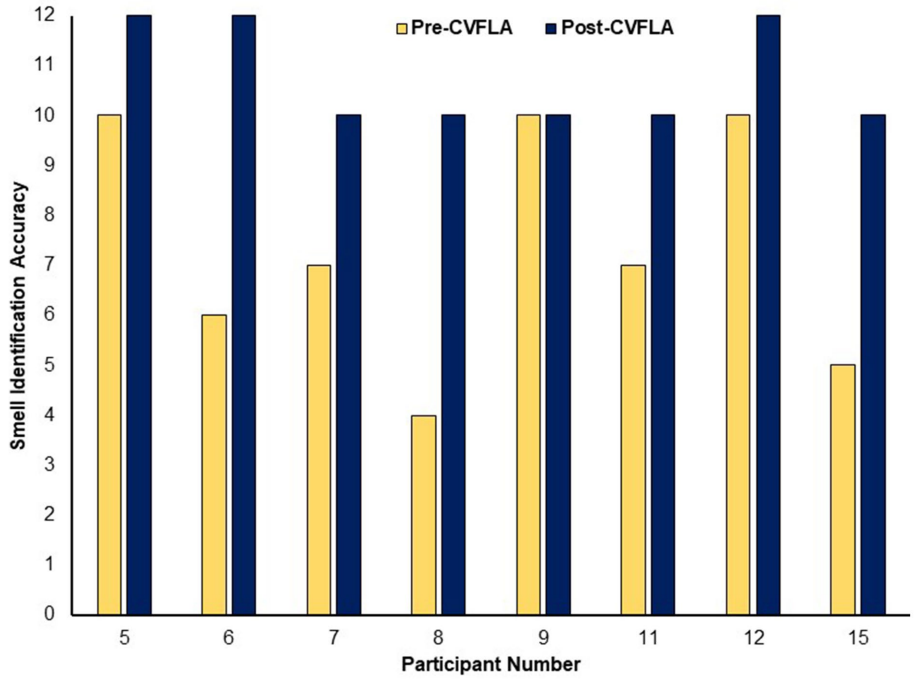

FIGURE 3
Objective (ODOFIN test) assessment of smell identification accuracy before and after the CVFLA intervention. With the 12 Sniffin' Sticks test, scores 0–6 indicate anosmia, scores 7–10 indicate hyposmia, and scores 11–12 indicate normosmia.

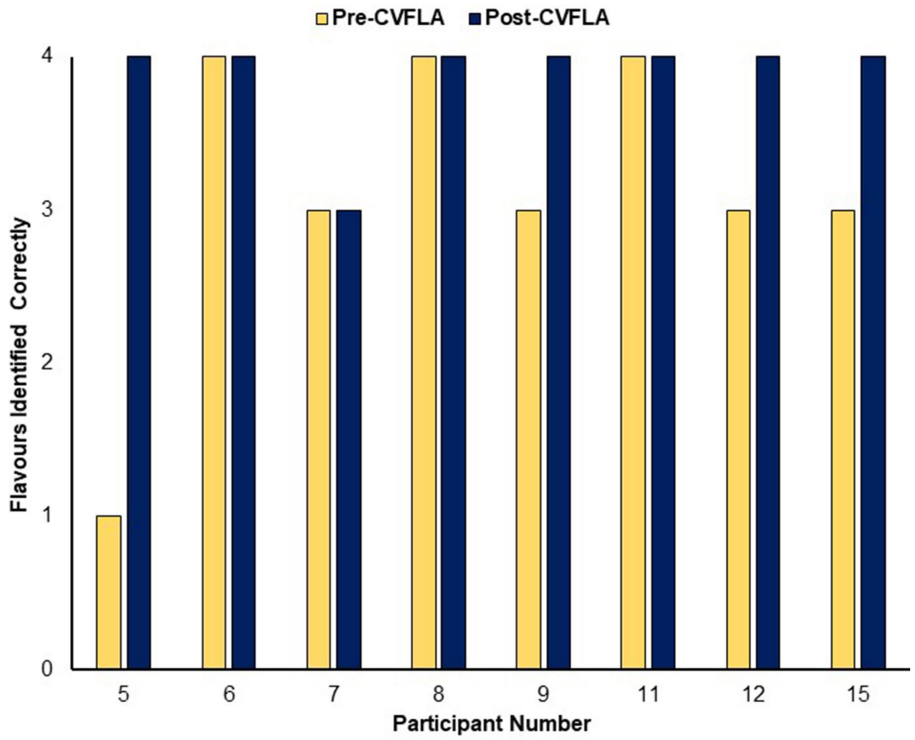

FIGURE 4
Objective (ODOFIN test) assessment of taste identification accuracy before and after the CVFLA intervention.

their known roles in episodic memory (hippocampus; Danieli et al., 2023), interoceptive awareness (insula; Craig, 2009; Evrard, 2019), and recall of self-related information (posterior cingulate; Morel et al., 2014). Another factor deserving some comment in the context of our study is the use of breathing exercises during the intervention sessions that may have contributed, at least partly, to the observed smell and

taste improvement, given recent evidence for respiration-driven normalization of the olfactory cortex (Gonzalez et al., 2023).

The present study had a number of limitations. First, the study involved only 15 participants and four of these participants did not complete their final in-person post-intervention assessments. Second, it cannot be ruled out that some improvement in taste and smell, especially in participants who had less than eight weeks of impairment, occurred simply with time (independent of 5–10 weeks of receiving CVFLA), although a noticeable improvement was also present in participants who had smell and taste impairment for more than six months, and all participants subjectively reported that the CVFLA intervention was helpful to them. Third, some participants reported practicing smelling and tasting in front of a mirror in between intervention sessions which may have potentially introduced a confound. Fourth, we did not use the complete Sniffin' Sticks Extended test which may have provided a more detailed assessment of the olfactory function and, in addition, complete pre- and post-CVFLA data on ODOFIN test assessment of smell and taste identification accuracy were available for only 8 of the 15 participants due to late arrival of the test kit or missed final in-person follow-up assessment for various reasons. Lastly, the intervention may be more beneficial for the recovery of smell than taste or, alternatively, the recovery of taste may follow smell recovery. A longer follow-up of the participants in further studies may help to clarify this as well as any secondary effects on mental health that may follow a different time course.

In conclusion, the new CVFLA intervention tested in this proof-of-concept study showed a very high level of acceptability and appeared to be a promising powerful tool to improve smell and taste. Further studies involving larger samples and appropriate control groups are required to confirm the effectiveness of this new intervention in improving smell and/or taste impairment in relevant non-clinical and clinical groups and to examine potential mediators and moderators of its effectiveness.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS) Brunel University London. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VK and JB contributed to conceptualization of the study and funding acquisition. SC contributed to research design, participant recruitment, intervention delivery, data acquisition, manuscript creation, and review and editing. KV contributed to data acquisition and scoring, and manuscript review and editing. EA contributed to project administration, and manuscript review and editing. VK contributed to project administration, research design, data analysis, manuscript creation, and review and editing. JB contributed to staff training for intervention delivery. All authors have reviewed the manuscript prior to submission.

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Conflict of interest

JB was employed by Learning JBE Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Assessment of COVID-19-related olfactory dysfunction and its association with psychological, neuropsychiatric, and cognitive symptoms

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Purpose of review: To provide a detailed overview of the assessment of COVID-19-related olfactory dysfunction and its association with psychological, neuropsychiatric, and cognitive symptoms.

Recent findings: COVID-19-related olfactory dysfunction can have a detrimental impact to the quality of life of patients. Prior to the COVID-19 pandemic, olfactory and taste disorders were a common but under-rated, under-researched and under-treated sensory loss. The pandemic has exacerbated the current unmet need for accessing good healthcare for patients living with olfactory disorders and other symptoms secondary to COVID-19. This review thus explores the associations that COVID-19 has with psychological, neuropsychiatric, and cognitive symptoms, and provide a framework and rationale for the assessment of patients presenting with COVID-19 olfactory dysfunction.

Summary: Acute COVID-19 infection and long COVID is not solely a disease of the respiratory and vascular systems. These two conditions have strong associations with psychological, neuropsychiatric, and cognitive symptoms. A systematic approach with history taking and examination particularly with nasal endoscopy can determine the impact that this has on the patient. Specific olfactory disorder questionnaires can demonstrate the impact on quality of life, while psychophysical testing can objectively assess and monitor olfaction over time. The role of cross-sectional imaging is not yet described for COVID-19-related olfactory dysfunction. Management options are limited to conservative adjunctive measures, with some medical therapies described.

KEYWORDS

olfactory disorders, olfaction, anosmia, COVID-19, hyposmia

Introduction

Coronavirus disease 2019 (COVID-19), a highly contagious viral illness caused by SARS-CoV-2, resulted in a global pandemic and more than 6.8 million deaths worldwide to date (WHO, 2023). SARS-CoV-2 is an enveloped positive single stranded RNA (+ssRNA) virus, which primarily is transmitted via exposure to respiratory droplets carrying the infectious virus from

close contact, or from droplet transmission from pre-symptomatic, asymptomatic or symptomatic individuals incubating the virus (Cascella et al., 2022). Whilst COVID-19 is predominantly considered a respiratory and vascular illness, emerging reports early in the pandemic identified the presence of sudden olfactory loss (anosmia or hyposmia) as being prevalent in patients with COVID-19 (Menni et al., 2020; Parma et al., 2020; Vetter et al., 2020; Gerkin et al., 2021). Despite there being a long association between olfactory and taste disorders during and after viral upper respiratory tract infections including influenza, parainfluenza, rhinoviruses and endemic coronaviruses (Suzuki et al., 2007), it is estimated that the prevalence of anosmia and dysgeusia is 10.2 fold higher and 8.6 fold higher, respectively, in COVID-19 patients when compared to other viral upper respiratory tract infections (Mutiawati et al., 2021). Furthermore, to date there has been over 755 million cumulative COVID-19 cases worldwide, with millions of patients now living with new onset olfactory and taste disorders (Parma et al., 2020; Cecchetto et al., 2021; Mutiawati et al., 2021; Ohla et al., 2022; WHO, 2023).

In addition to the acute symptoms of COVID-19, there are individuals that have the prevalence of these symptoms lasting longer than 12 weeks – this syndrome being termed "long COVID." Data from the United Kingdom (UK) Census 2021, run by the Office for National Statistics (ONS), places the prevalence of long COVID within the UK population as being between 3.0 to 11.7% (Gokani et al., 2022). Groups at higher risk of developing long COVID include women, those aged 35–49 years old, Caucasian ethnicity or those living with disabilities (Ayoubkhani et al., 2021; Gokani et al., 2022; Ohla et al., 2022).

Prior to the emergence of COVID-19, olfactory and gustatory disorders were a common but under-researched, under-treated and under-rated sensory loss but increasing evidence has shown that anosmia (complete loss of smell) is as an independent risk factor for reduced longevity in this patient cohort (Pinto et al., 2014; Laudisio et al., 2019; Liu et al., 2019). This disease brings with it novel challenges and also highlights and exacerbates the current unmet need for accessing good healthcare for these patients living with olfactory disorders and other symptoms secondary to COVID-19 (Ball et al., 2021). This article thus explores the associations that COVID-19 has on psychological, neuropsychiatric, and cognitive symptoms, and provide a framework and rationale for the assessment of patients presenting with COVID-19 olfactory dysfunction.

COVID-19 associations

Cognitive symptoms

Coronaviruses, the broad family of viruses that the SARS-CoV-2 virus belongs to, is one of many pathogens known to cause post-infectious olfactory dysfunction (Suzuki et al., 2007). Nasal epithelial cells show relatively high expression of the angiotensin-converting enzyme 2 (ACE-2) receptor, which is required for the entry of SARS-CoV-2 (Sungnak et al., 2020; Song et al., 2021). SARS-CoV-2 thus can enter the Central Nervous System (CNS) through the olfactory nerve which is the only cranial nerve in contact with the environment. Viral damage of the olfactory bulb may be the first insult needed for further degeneration to occur (Song et al., 2021; Kay, 2022). In the acute phase of COVID-19 infection, autopsy studies have identified the prevalence of neuroinflammation, activation of microglia, neuronal death, and meningeal hyperaemia in post-mortem cortex tissues of COVID-19 patients (Boroujeni et al., 2021; Colombo et al., 2021).

Other hypotheses in literature have been proposed for SARS-CoV-2 route of entry into the CNS. A proposed haematogenous route, which is adopted by coronaviruses and other viruses, include the infection of leucocytes by the virus which allows it to be transported across the blood brain barrier (Koyuncu et al., 2013; Nagu et al., 2021). Consequently, neuroinflammation occurs by the triggered release of proinflammatory chemokines and cytokines resulting in increased blood brain barrier permeability and the easier facilitation of SARS-CoV-2 entry into the CNS (Koyuncu et al., 2013; Nagu et al., 2021). An enteric route has also been proposed, whereby SARS-CoV-2 entry into the CNS occurs as a result of there being a direct connection of the enteric nervous system with the brain via the vagus nerve (Gao et al., 2020). All the routes proposed involve the binding of the SARS-CoV-2 spike protein with the ACE-2 receptor on target cells thus facilitating the entry of the virus into the CNS (Gao et al., 2020; Sungnak et al., 2020; Nagu et al., 2021; Song et al., 2021).

Moreover, studies have reported long term CNS involvement and the prevalence of cognitive impairment in long COVID infection ranging from 25 to 50% (Miners et al., 2020; Miskowiak et al., 2021; Rahman et al., 2021; Chen et al., 2022). One proposed theory for the persistent cognitive impairment seen in long COVID may be secondary to the presence of viral RNA in the brain of long COVID patients and persistent systemic inflammation (Stein et al., 2022; de Paula et al., 2023). Furthermore, structural brain changes found in long COVID anosmic patients include lower concentration of grey matter in the amygdala, insular cortex, parahippocampus, frontal orbital gyrus, olfactory cortex, caudate and putamen (Miners et al., 2020; Campabadal et al., 2023). Other structural changes seen include medial temporal lobe dysfunction involving the hippocampus (Llana et al., 2022), entorhinal and perirhinal cortex (Douaud et al., 2022). The medial temporal lobe is important in multiple cognitive processes including semantic memory and processing of emotions and is also one of the first regions to atrophy in Alzheimer's disease (AD). Semantic memory is long-term memory and relies heavily on the temporal lobe and structures such as the hippocampus and parahippocampus. At least 20% of patients with COVID-19-related olfactory dysfunction had impaired semantic memory (Gokani et al., 2022). Thus, semantic memory impairment seen in long COVID patients is similar in presentation to patients diagnosed with AD (Fiorentino et al., 2022). Other studies have reported additional impairments of executive functions, attention, memory, information processing and fatigue after acute COVID-19 infection (Braga-Paz et al., 2022; Fiorentino et al., 2022; de Paula et al., 2023). It appeared that these symptoms persisted and were more common after follow up at 4 months.

One study comparing patients with chronic fatigue syndrome with patients with long COVID brain fog showed similarity in cognitive patterns between the two groups (Azcue et al., 2022). Although the underlying neuronal substrate is unknown for chronic fatigue, hypothalamic changes which has been observed in chronic fatigue syndrome and myalgic encephalitis may be responsible for long COVID brain fog (Carruthers et al., 2011). Thus, this implies that SARS-CoV-2 is neuroinvasive and may remain in the brain tissue causing neuroinflammation which increases cognitive burden (Stein et al., 2022; de Paula et al., 2023).

COVID-19-related olfactory dysfunction can be a marker of impending cognitive dysfunction. Further large high quality cohort studies investigating the genetic and biomarkers between cognitive dysfunction, anosmia and severity of acute COVID-19 infection are needed. Future studies should also focus on prevention and identifying at risk patients of cognitive dysfunction within this cohort.

Neuropsychiatric symptoms

Olfactory dysfunction is a known early sign of many neuropsychiatric disorders, particularly AD and Parkinson's Disease (Yoo et al., 2018; Rebholz et al., 2020; Cristillo et al., 2021; Azcue et al., 2022). It is hypothesized that the neurodegenerative patterns seen in these disorders begin in the olfactory bulb, which is susceptible to damage from inflammatory processes triggered by viral neuroinvasion (Attems et al., 2014; de Erausquin et al., 2021). Furthermore, COVID-19-related olfactory dysfunction, and the observed pattern of degeneration in the olfactory bulb and limbic brain regions, is similar to that seen in the early stages of AD and Lewy body disease (Kay, 2022). Notably olfactory loss, and many neuropsychiatric disorders are associated with high levels of interleukin-6 (IL-6), an inflammatory marker which is also implicated in the cytokine storm in COVID-19 patients (Gialluisi et al., 2020; de Erausquin et al., 2021). In addition to increased IL-6 levels, an increase in levels of C-Reactive Protein (CRP), IL-1β, IL-2 and Tumour Necrosis Factor (TNF) has been observed in both acute COVID-19 patients and Parkinson's patients, which may imply that high levels of these markers (as seen in the COVID-19 cytokine storm) are associated with a higher clinical severity risk of Parkinsonian symptoms in acute COVID-19 patients (Qin et al., 2016; Qiu et al., 2019; Gialluisi et al., 2020; de Erausquin et al., 2021). This inflammatory process may have the potential to induce neurological damage such as encephalitis (Gialluisi et al., 2020). The use of IL-1 and IL-6 receptor antagonists such as tociluzimab has been seen to reduce the severity of acute COVID-19 illness in patients, which in turn may reduce the neurological damage that occurs secondary to the cytokine storm (Ghofrani Nezhad et al., 2023).

Moreover, acute COVID-19 and neuropsychiatric disorders share common risk factors such as APOE4 allele homo/heterogeneity, increased age, sex, hypertension, diabetes mellitus and obesity (Ortiz et al., 2022). Apolipoprotein 4 (APOE4) allele homogeneity or heterogeneity may lead to potential cerebrovascular dysfunction and neuroinflammation blood brain barrier leakiness (Zhang and Xie, 2020; Ortiz et al., 2022). Furthermore, the SARS-CoV-2 N protein has been shown to inhibit RIG-1-like pathway. RIG-1 (retinoid acid-inducible gene-1) has been found to have associations with schizophrenia suggesting that coronavirus infection could lead to exacerbation of previous neuropsychiatric illness (Rhoades et al., 2022). Moving forward, more research is required to clarify the exact mechanisms underlying the associations between COVID-19-related olfactory dysfunction and neuropsychiatric disorders.

Psychological symptoms

Psychological impacts are associated with both acute COVID-19 infection and long COVID. In the acute setting, acute COVID-19 infection has been associated with negative feelings and behaviors such as anxiety, stress, anger, avoidance, and isolation (DeJong et al., 2020). In a cohort study of 461 patients hospitalised with acute COVID-19 infection, Kim et al. (2021) identified the presence of symptoms such as anxiety (16.3%), depression (26.5%), insomnia (33.4%), and suicidal ideation (11.7%). These symptoms significantly improved in the week following hospitalisation (Kim et al., 2021). A fluorodeoxyglucose positron emission tomography (FDG-PET) study on acute COVID-19 patients suggests the increased presence of these psychological symptoms being due to COVID-19-related dysfunction of the cingulate cortex, an anatomical area involved in the processing of emotions, decision making, memory and depression (Hugon, 2022). Studies in literature have also observed high levels of various cytokines that are raised in patients infected with SARS-CoV-2, such as IL-6, TNF-α, IL-1β and ferritin in patients with psychiatric disorders such as depression, post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD) (Ma et al., 2010; Parker et al., 2015; Lindqvist et al., 2017; Karagüzel et al., 2019). Furthermore, pathological analysis of autopsy specimens of patients with acute COVID-19 infection has identified that Neurolipin-1 (NRP-1) is expressed in olfactory epithelial cells and can potentiate SARS-CoV-2 infectivity and provide a route for CNS penetration of the virus (Cantuti-Castelvetri et al., 2020).

Long COVID also has significant psychological associations. In the 3 months following acute COVID-19 infection, patients are at increased risk of mood and anxiety disorders. Taquet et al. (2021) identified that 5.8% of patients had a new psychiatric diagnosis in the 14–90 days after COVID-19 infection in a retrospective study of 62 354 COVID-19 cases in the USA (Taquet et al., 2021). However, this relationship is complex, with patients with pre-existing psychiatric disorders also at a potential increased risk of long COVID (Kataoka et al., 2023). Studies have also suggested that the psychological impact of acute and long COVID is associated with the severity of the initial acute COVID-19 infection. A prospective cohort study in 6 European countries of 247,249 adults, including 9,979 with COVID-19, found a higher prevalence of depression and poor sleep quality amongst individuals with COVID-19, with an increased risk of depression amongst patients who were bedridden for more than 7 days (Magnúsdóttir et al., 2022). Tackling psychological symptoms should be a priority area of focus for survivors of COVID-19 due to the increased incidence of mental health disorders when compared to patients hospitalised for other causes or similar infections such as seasonal influenza (Xie et al., 2022).

Figure 1 below summarises the proposed mechanisms of destruction in acute COVID-19 infection and its downstream effects on the limbic system and its resulting cognitive, neuropsychiatric, and psychological symptoms.

Assessment of COVID-19 olfactory dysfunction

Clinical features of long COVID

The continuing presence of olfactory dysfunction and the potential for it to become permanent sequelae in the context of patients with long COVID presents a problem to clinicians worldwide (Gokani et al., 2022; Mendes Paranhos et al., 2022).

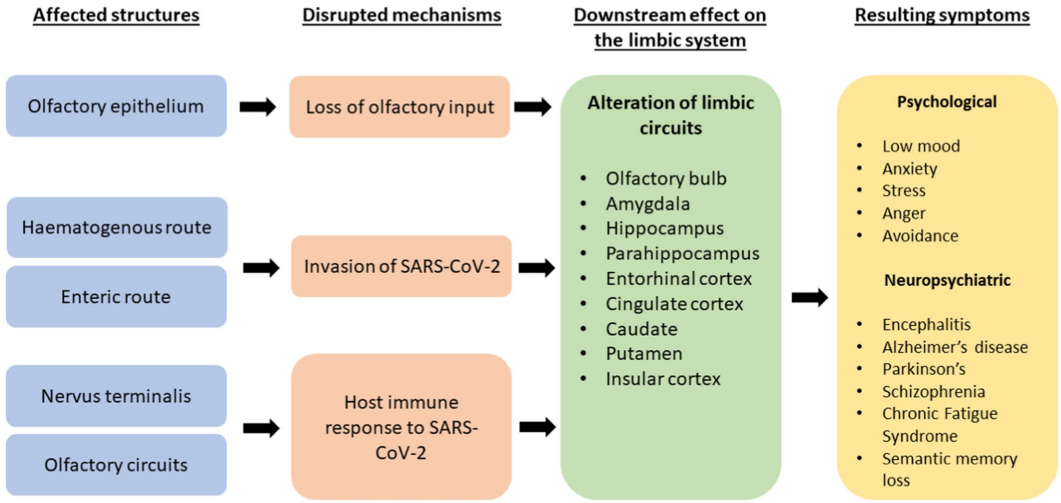

FIGURE 1
A flowchart explaining proposed mechanisms of destruction by SARS-CoV-2 and its effects on the limbic system and resultant effects on psychological, neuropsychiatric and cognitive symptoms.

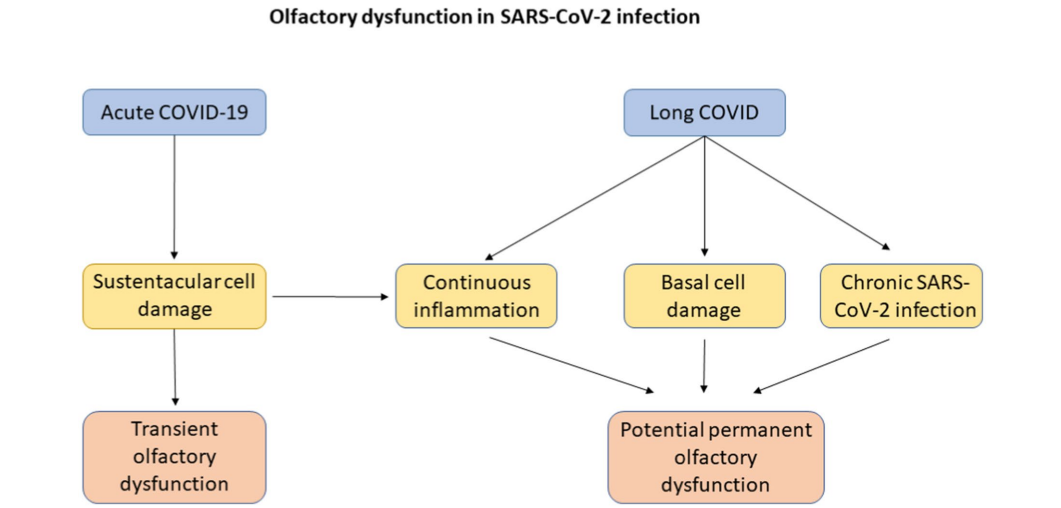

FIGURE 2
A flowchart explaining possible mechanisms of olfactory dysfunction in acute COVID-19 infection and in long COVID with its eventual progression to transient or potential permanent olfactory dysfunction.

Olfactory dysfunction in acute COVID-19 infection tends to be transient, lasting around 2–3 weeks and may be partially explained by SARS-CoV-2 having a high affinity for the sustentacular cells of the olfactory epithelium that express ACE-2 and that these cells possess substantial capacity for repair and regeneration after damage (Doty, 2021; Mendes Paranhos et al., 2022). Long term prevalence of olfactory dysfunction may be secondary to continuous inflammation, damage to basal cells and chronic SARS-CoV-2 infection in the olfactory epithelium (Liang and Wang, 2021). Chronic inflammation could result in gene expression modulation which in turn can alter the function of olfactory epithelium basal cells from neural regeneration to inflammatory signalling and immune cell proliferation (Chen et al., 2019). This has been highlighted in Figure 2.

Olfactory dysfunction history and examination

A thorough history is required to establish the nature of olfactory dysfunction which patients are suffering from, and the extent to which their quality of life has been affected. Firstly, it is crucial to differentiate whether the patient has anosmia, hyposmia, phantosmia, or parosmia. Next, establishing a timeline of their symptoms will help identify what their smell was like before, any events that may have triggered these symptoms (besides an acute COVID-19 infection), and how they have developed over time (Luke et al., 2022).

It is important to look out for other potential causes of olfactory dysfunction. These include sinonasal disorders such as chronic rhinosinusitis, previous head trauma, surgery, or neurodegenerative

disorders. Conducting a full review of all body systems will help uncover any other symptoms of long COVID. Furthermore, it is important to elicit the patient's drug history, as many common medications are known to cause olfactory dysfunction (Schiffman, 2018). Finally, whether the patient has history of smoking, and any occupational exposure to certain hazardous chemicals is also important, as these can cause olfactory dysfunction (Schiffman, 2018; Werner and Nies, 2018).

After recording the olfactory dysfunction history, an examination of the nose is essential. Direct visualisation using fine nasal endoscopy will allow assessment of the nose, nasopharyngeal space, and olfactory cleft to rule out any causes of conductive olfactory loss (Seiden and Duncan, 2001). If the history from the patient raises suspicion of a sensorineural cause of olfactory dysfunction, a full cranial nerve examination is warranted.

Investigating COVID-19-related olfactory dysfunction

Subjective assessments such as the Olfactory Disorders Questionnaire (ODQ) can be useful in establishing the degree of olfactory dysfunction and the impact to patients' quality of life (Langstaff et al., 2019; Garden et al., 2023), as well as help identify qualitive symptoms such as phantosmia and parosmia.

As olfaction plays a major role in flavor perception, many patients may report a disturbance in their sense of taste. However true gustatory loss is rare and their perception of "loss" of their sense of taste is due to their olfactory dysfunction affecting retronasal olfaction (Wrobel and Leopold, 2004). Gustatory testing using Taste Strips may be a quick way in ruling out true gustatory loss. It involves using strips of filter paper consisting of four different flavours (sweet, sour, salty, bitter) in various concentrations. These strips are placed on the tongue of patients, and they are asked to identify which of the four flavours they think it is (Mueller et al., 2003).

Psychophysical olfactory testing can be performed to quantitatively measure olfactory function and confirm the presence of olfactory dysfunction (Hummel et al., 2016; Luke et al., 2022). Olfaction can be assessed orthonasally or retronasally; odours can be sniffed through the nostrils (orthonasal olfaction) or allowed to enter through the nasopharynx through the use of powders (retronasal olfaction) (Croy et al., 2014; Hummel et al., 2016; Goldberg et al., 2018). Objective testing of orthonasal olfaction can be done by using common validated psychophysical tests such as the Sniffin' Sticks test, University of Pennsylvania Identification Test (UPSIT), the Toyota & Takagi Olfactometer, the Cross-Cultural Smell Identification Test, the Brief Smell Identification Test or the Connecticut Chemosensory Clinical Research Center (CCCRC) test (Doty et al., 1984, 1996; Cain et al., 1988; Kobal et al., 1996; Kondo et al., 1998; Menon et al., 2013; Hummel et al., 2016; Hutson et al., 2022). These tests have been established in objectively assessing the degree of olfactory dysfunction, categorizing patients into normosmia, hyposmia or anosmia (Doty et al., 1984, 1996; Cain et al., 1988; Kobal et al., 1996; Kondo et al., 1998; Menon et al., 2013; Hummel et al., 2016; Hutson et al., 2022). While the UPSIT test can be performed by the patient on their own, the Sniffin' Stick Test requires a medical professional to administer the test. Therefore, the choice of which test to use is up to the resources and capacity of the clinic the patient is being assessed. Retronasal psychophysical testing can be performed in patients where there is a perceived mismatch between orthonasal and retronasal olfaction that is not accounted for by a gustatory component (Heilmann et al., 2002; Croy et al., 2014; Goldberg et al., 2018; Luke et al., 2022). The most common retronasal olfaction technique is the retronasal olfaction test (ROT) (Heilmann et al., 2002). This involves the placement of twenty food powders onto the tongue using squeezable plastic vials, whilst the subject's nose is clipped. A forced-choice odour identification test method (whereby a suprathreshold odour is presented to a subject whom must identify the odour from a list of descriptors) is used with four possible options and responses recorded (Heilmann et al., 2002).

It Is important for clinicians to utilise a psychophysical test that is appropriately and culturally adapted for the subject population identified to obtain results that are reliable (Rombaux et al., 2009; Frasnelli et al., 2010; Patel et al., 2022). Furthermore, increased length of the screening testing is associated with increased reliability and validity of the results (Doty et al., 1995). Consequently, it is recommended that short screening tests be used for identification of subjects with olfactory dysfunction whereby longer tests be used to quantitatively assess the degree of olfactory dysfunction (Hummel et al., 2016; Luke et al., 2022; Patel et al., 2022).

As mentioned earlier, patients with acute COVID-19 infection and long COVID may suffer from anxiety and depression. Furthermore, patients who suffer from smell and taste disorders suffer higher rates of anxiety and depression compared to the general population. Thus, it may be beneficial in asking patients to complete validated questionnaires such as the Patient Health Questionnaire Anxiety and Depression scale to identify those who are suffering from depression and anxiety (Erskine and Philpott, 2020). A referral to the relevant mental health services can then be made.

The role of cross-sectional imaging in investigating COVID-19-related olfactory dysfunction

The role of cross-sectional imaging in the context of COVID-19-related olfactory dysfunction has yet to be established (Whitcroft and Hummel, 2020). Computerized Tomography (CT) imaging of the paranasal sinuses and brain may be performed to exclude sinonasal or intracranial abnormalities (including malignancies) (Lund and Mackay, 1993; Higgins and Lane, 2014). Generally, structural Magnetic Resonance Imaging (MRI) has many uses in the assessment of olfactory disorders, as it allows for the assessment of the olfactory apparatus, the exclusion of asymptomatic chronic inflammation of the paranasal sinuses, the assessment of neurodegenerative disorders, the characterisation of traumatic brain injuries and the exclusion of intracranial or sinonasal neoplasms (Decker et al., 2013; Higgins and Lane, 2014; Luke et al., 2022). However, there is limited evidence to suggest a role for this modality in the context of post-infectious olfactory disorder (Hutson et al., 2022).

Olfactory dysfunction management

Addison et al. (2021) provided an evidence-based practical guide for the management of post-infectious olfactory dysfunction, including COVID-19-related olfactory dysfunction (Addison et al., 2021). The Clinical Olfactory Working Group members emphasized

the recommendation for olfactory training; a non-surgical and non-pharmacological approach to manage COVID-19-related olfactory dysfunction. Other key medical management options were discussed including steroids and vitamin A, but they highlighted the need for further research to confirm the place for the varying therapeutic options available.

Adjunctive treatments

There are limited treatment options available for persistent COVID-19-related olfactory dysfunction as this is a relatively novel condition (Whitcroft and Hummel, 2020). However, there are numerous adjunctive management options used for post-viral olfactory dysfunction that could be used for patients who suffer from persistent olfactory dysfunction, including simple lifestyle measures, olfactory training, and traditional Chinese acupuncture (TCA).

The olfactory system is closely linked to the limbic system (Albrecht and Wiesmann, 2006). Consequently, olfactory dysfunction is associated with a deterioration in the quality of life, social skills, relationships and mental wellbeing of this patient cohort (Saniasiaya and Prepageran, 2021). Patients with olfactory dysfunction, including COVID-19-related olfactory dysfunction, report a decrease in flavour perception due to impaired retronasal olfaction (Nordin et al., 2011). This is associated with loss of or reduced appetite, as well as diminished food enjoyment (Elkholi et al., 2021; AlShakhs et al., 2022). Scheduled eating hours may address the dysregulated appetite observed (Croy et al., 2014). In addition, COVID-19-related olfactory dysfunction has been linked to depression and patient isolation (Coelho et al., 2021; AlShakhs et al., 2022). This association may be explained by the overlap between the brain areas involved in olfaction and depression, notably the orbitofrontal cortex, anterior and posterior cingulate cortices, insula, amygdala, hippocampus and thalamus (Seo et al., 2010; Marine and Boriana, 2014). Social support groups such as Fifth Sense and AbScent can play an important role in facilitating patients to emotionally accept their olfactory deficit, allowing patients to perform adaptive adjustments to their lives living with this disease (Nordin et al., 2011; Saniasiaya and Prepageran, 2021).

It is also well recognised that patients with olfactory dysfunction have concerns regarding personal safety and hygiene (Philpott and Boak, 2014). Patients with olfactory dysfunction are significantly more likely to be involved in more household accidents compared to normosmic individuals (Croy et al., 2012). Simple lifestyle measures that patients can do to keep themselves and co-habitants safe include maintaining smoke and natural gas detectors and monitoring food expiry dates and nutritional intake (Whitcroft and Hummel, 2020).

There is evidence that olfactory training (OT) is an effective and frequently used treatment option for patients with hyposmia or anosmia secondary to various aetiologies (Pekala et al., 2016; Sorokowska et al., 2017). It involves patients receiving repeated exposure to different odours over time to help improve their olfactory sensitivity (Altundag et al., 2015). Specifically, the odours typically used in OT include phenylethyl alcohol (rose scent), eucalyptol (eucalyptus scent), citronella (lemon scent) and eugenol (clove scent) (Hummel et al., 2009). Standard OT involves patients sniffing these odours (present on cotton pads within containers) twice daily for at least 20–30 s for each scent. (Kronenbuerger and Pilgramm, 2023). Hura et al. (2020) conducted a review of the treatments of post-viral olfactory dysfunction which showed OT is recommended to improve olfactory outcomes with higher concentrations, longer duration of OT and a wide variety of odours to be the most effective (Hura et al., 2020). Furthermore, OT over 4 weeks has been demonstrated to improve subjective and psychophysical testing scores in patients with persistent COVID-19-related olfactory dysfunction (De AT et al., 2022). OT is a low-cost adjunctive therapy with negligible adverse effects for patients with persistent COVID-19-related olfactory dysfunction (Whitcroft and Hummel, 2020).

TCA is a popular complementary therapy that is used for a wide variety of conditions. There have been studies investigating its use in otorhinolaryngological conditions such as allergic rhinitis, tinnitus, and sudden sensorineural hearing loss. However, there is a paucity of high-quality evidence to demonstrate its benefit (Kahn et al., 2020). There are a few studies demonstrating a possible improvement in psychophysical assessment scores with TCA in patients with post-viral olfactory loss but these have small sample sizes (Vent et al., 2010; Dai et al., 2016). To date, there is no research conducted examining the efficacy of TCA on COVID-19-related olfactory dysfunction. TCA is performed by the placement of needles in acupoints by trained professionals, with these needles kept in place for 20 min. TCA is administered 3 times a week, with each course lasting 10 sessions. There are 3–5 days of rest in between courses, and courses are repeatedly administered until the patient has received 3 months in total (Vent et al., 2010; Dai et al., 2016). Similar to OT, TCA is a cost effective, low risk complementary therapy that may benefit patients, but further research is needed to determine its efficacy in post-viral olfactory loss and COVID-19-related olfactory dysfunction.

Pharmacological treatments

For COVID-19-related olfactory dysfunction that does not resolve spontaneously, pharmacological intervention may be indicated. A Cochrane review on intervention of persistent COVID-19-related olfactory dysfunction has highlighted the significant lack of evidence exploring the efficacy and harms of treatment for patients with COVID-19-related olfactory dysfunction (Webster et al., 2022).

Intranasal and oral corticosteroids

Huart et al. (2021) have recently published an international expert group viewpoint that there is currently no evidence for the use of intranasal or oral corticosteroids in COVID-19-related olfactory dysfunction (Huart et al., 2021). Current literature is often underpowered and any evidence supporting the use of corticosteroids is weak (Saussez et al., 2021; Kim et al., 2022; Schepens et al., 2022). Furthermore, there is sufficient evidence that even limited systemic corticosteroid treatment can have harmful side-effects, such as increased risk of hip fractures and decompensating glaucoma (Yasir et al., 2022).

Non-steroidal pharmacological management

Vitamin A

It has been theorised that vitamin A will encourage regeneration of olfactory epithelium. This is because vitamin A is converted to

retinoic acid, which is thought to control olfactory progenitor cell differentiation, and can thus prevent exhaustion of stem cell supply or accumulation of non-functional immature neurones (Paschaki et al., 2013). At present, there has been no RCT that has examined the efficacy of intranasal vitamin A specifically on patients with COVID-19-related olfactory dysfunction. Promisingly, a pseudo-randomised clinical trial showed than in 124 patients with post-viral olfactory loss, a minimum clinically important difference in olfactory function was seen in 37% of those receiving intranasal vitamin A compared with 23% receiving smell training alone (Hummel et al., 2017). However, due to the unbalanced treatment groups and pseudo-randomisation, the study lacked scientific rigor that is required for further proof of concept evidence for intranasal vitamin A. There is currently an ongoing double blind randomised controlled trial (RCT), APOLLO, which aims to further explore the use of intranasal vitamin A drops in the treatment of post-viral olfactory loss (ISRCTN - ISRCTN13142505, n.d.). This in turn will provide further baseline information for this treatment option to be investigated for patients with COVID-19-related olfactory dysfunction.

Platelet rich plasma

Platelet rich plasma (PRP) is an autologous blood product, with supraphysiologic concentration of growth factors, and can be used in peripheral nerve regeneration. Several studies have indicated that PRP administered intravenously may be effective in improving olfactory outcomes in patients following acute COVID-19 infection (Steffens et al., 2022; Wang et al., 2022; Lechien et al., 2023); including a recent randomised controlled trial which found that patients receiving PRP injection resulted in a 3.67 increase in Sniffin' Sticks score compared with the placebo (95% CI 0.05–7.29; $p = 0.047$) (Yan et al., 2023). However, findings were significantly underpowered with only 26 participants completing the study. Two of the studies found no adverse effects were reported, however Lechien et al. (2023) reported transient epistaxis (n = 31), parosmia related to the xylocaine spray ($n = 10$) and vasovagal episode ($n = 2$) (Lechien et al., 2023). Findings may therefore suggest that PRP could be a helpful tool in managing COVID-19-related olfactory dysfunction, however larger randomised trials are required.

Theophylline

Theophylline is a drug derived from methylxanthine, with it having systemic properties including smooth muscle relaxation, bronchial dilatation, and diuresis as well as having a stimulant effect on the cardiac and central nervous systems (Jilani et al., 2023). Clinically, theophylline is widely used in various obstructive respiratory pathologies including Chronic Obstructive Pulmonary Disease (COPD), asthma and infant apnoea (Jilani et al., 2023). In the context of anosmia, theophylline is suggested to improve olfactory neuroepithelium regeneration, by inhibiting phosphodiesterase and increasing secondary messengers (such as cyclic adenosine monophosphate and cyclic guanosine monophosphate) (Henkin et al., 2009, 2011). A RCT evaluating the impact of intranasal theophylline on patients with post-viral olfactory dysfunction initially indicated that there was no significant improvement in smell between the theophylline group compared with the placebo saline irrigation (Lee et al., 2022). However, authors hypothesized that the dosage of theophylline could be safely elevated, and thus conducted a phase 2 trial specifically on patients with COVID-19-related olfactory dysfunction (Gupta et al., 2022). At the higher dose, mixed model analysis revealed that the change in UPSIT score was not significantly different between the two groups. These findings were limited by the small sample size of 45 participants and the use of subjective assessments of olfactory dysfunction. Larger studies, using more objective testing methods, are warranted to further investigate the impact and efficacy of intranasal theophylline on patients with COVID-19-related olfactory dysfunction.

Ultramicronized palmitoylethanolamide and luteolin supplements

Ultramicronized palmitoylethanolamide and luteolin (PEA-LUT) are anti-inflammatory and neuroprotective agents. One hypothesis is that COVID-19-related olfactory dysfunction may be due to neuroinflammatory results within the olfactory bulb and central nervous system, therefore PEA-LUT may have a potential role in its management. A RCT of 185 patients with COVID-19-related olfactory dysfunction found that those treated with PEA-LUT oral supplements plus olfactory training showed significantly greater improvement in Sniffin' Sticks score compared with controls (Di Stadio et al., 2022). By the 90-day endpoint, there was greater than a ten-fold prevalence of anosmia in the control versus intervention. Although providing promising results, further longitudinal studies are required for clarifying optimal timing and dosing parameters of PEA-LUT for patients with limited or absent recovery from COVID-19-related olfactory dysfunction and to also evaluate the effect of PEA-LUT on neuroinflammation by measuring specific neuroinflammatory biomarkers.

Zinc sulphate

Zinc is an important trace metal in the human body, and it regulates the differentiation, proliferation, maturation and function of lymphocytes and other leucocytes (Jeong and Eide, 2013; Gammoh and Rink, 2017; Abdelmaksoud et al., 2021). Consequently, it was hypothesised that zinc deficiency may contribute to COVID-19-related olfactory dysfunction due to these patients being more susceptible to severe acute COVID-19 infection and its associated complications. However, a recent study has found that serum zinc levels in patients with acute COVID-19 infection were not significantly different between those with the presence of or those with the absence of olfactory and/or gustatory dysfunction (Abdelmaksoud et al., 2021). Interestingly, they did find that the median duration of olfactory and/or gustatory dysfunction was significantly shorter in patients who received oral zinc supplements. Further longitudinal studies should be conducted to investigate the impact and efficacy of oral zinc supplements in the role of treating COVID-19-related olfactory dysfunction.

Buffer solutions

Free calcium plays a fundamental role in peripheral olfactory processing, including feedback inhibition. Thus, it is proposed that the reduction of intranasal free calcium with buffer solutions may improve olfactory function in patients with olfactory impairment (Whitcroft and Hummel, 2019). Examples of buffer solutions include sodium citrate, tetra sodium pyrophosphate (TSPP) and sodium gluconate, which are discussed below.

Sodium citrate

Sodium citrate administered intranasally can modulate the cascade of olfactory receptor transduction (Whitcroft and Hummel,

2019). At present there is currently no RCT investigating the efficacy of intranasal sodium citrate in patients with COVID-19-related olfactory dysfunction. However, an improvement in olfactory threshold was seen in a prospective placebo-controlled trial, whereby intranasal sodium citrate was trialled against intranasal sodium chloride treatment for 57 patients with olfactory loss (Whitcroft et al., 2016). Furthermore, in a prospective placebo-controlled trial with 49 patients exclusively with post-viral olfactory dysfunction, intranasal sodium citrate showed significant improvement in the compound threshold and ident cation scores but nil change in odour or threshold identification when compared to the placebo (Whitcroft et al., 2017). A single application of 0.5 mL of sodium citrate per nostril, compared to sterile water in a RCT of 55 patients with non-conductive olfactory dysfunction, was shown to have statistically significant improvement in olfactory function using olfactory thresholds for phenyl ethyl alcohol, 1-butanol, and eucalyptol, with thresholds measured up to 2 h post intervention (Philpott et al., 2017). It is proposed that the sodium citrate solution administered nasally binds to the free calcium ions in the nasal mucus, thus reducing the free calcium available in the nasal mucosa (Philpott et al., 2017). All the aforementioned studies lack robust long-term data as well as data specific to patients with COVID-19-related olfactory dysfunction, and this will need to be addressed in future RCTs in order to explore the clinical applications and efficacy of sodium citrate as a buffer solution in this patient cohort.

Tetra sodium pyrophosphate

Tetra sodium pyrophosphate (TSPP) is a calcium chelating agent that lowers calcium concentration (Shirashoji et al., 2016). Reduced calcium has been suggested to increase sensitivity to odorants, as shown utilising sodium citrate to improve olfactory function (Philpott et al., 2017). A randomised controlled trial, on 64 patients with COVID-19-related olfactory dysfunction, claimed to find that there was a statistically significant improvement in Sniffin' Stick scores between those treated with intranasal TSPP compared with sodium chloride, but the study was underpowered for the minimum clinically important difference in the Sniffin' Sticks (Abdelazim et al., 2022). This may be due to the role of intranasal TSPP as a chelating agent, as the TSPP group had a statistically significant lower nasal calcium concentration than those treated with sodium chloride. Larger, higher-powered studies will be required to further investigate the role of intranasal TSPP as a buffer solution in treating COVID-19-related olfactory dysfunction.

Sodium gluconate

Similarly, to TSPP, sodium gluconate has also shown to be a highly efficient chelating agent (Fiume et al., 2019). It has also shown some potential in the use to treat COVID-19-related olfactory dysfunction, with a statistically significant improvement in Sniffin' Stick scores in those receiving intranasal sodium gluconate at 1 month (Abdelazim and Abdelazim, 2022). As with TSPP, these studies are underpowered at best, and will require larger, well powered studies to investigate its efficacy as a buffer solution in improving olfactory function in this patient cohort.

Proposed algorithm for investigating COVID-19-related olfactory dysfunction

Utilising the aforementioned evidence, the authors propose an algorithm for clinicians to utilise when presented with patients with possible COVID-19-related olfactory dysfunction. This can be seen in Figure 3 below.

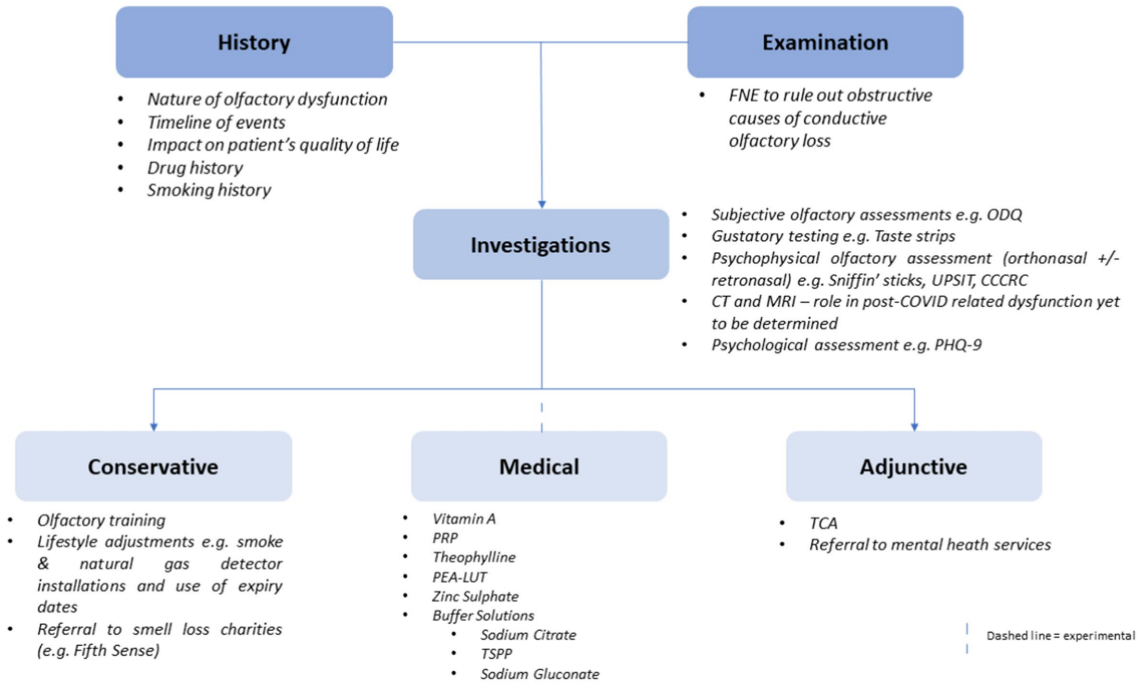

FIGURE 3
A flowchart illustrating a proposed algorithm for clinicians to follow when managing a patient with suspected COVID-19-related olfactory dysfunction.

In summary, the efficacy of the medical management of COVID-19-related olfactory dysfunction remains experimental at best, with studies for the different treatment strategies either being underpowered or not performed on patients with COVID-19-related olfactory dysfunction. Future larger, highly powered studies which utilises validated olfactory assessment scores will provide light on the efficacy of these treatments.

Conclusion

Acute COVID-19 infection and long COVID have strong associations with psychological, neuropsychiatric, and cognitive symptoms. A systematic and holistic approach with history taking and examination particularly with nasal endoscopy can determine the impact that COVID-19-related olfactory dysfunction has on the patient. Specific olfactory disorder questionnaires can demonstrate the impact on quality of life, while psychophysical testing can objectively assess and monitor olfaction over time. The role of cross-sectional imaging is not yet described for COVID-19-related olfactory dysfunction. Management options are limited to conservative adjunctive measures, with medical therapies having a yet unproven role in the treatment of this disorder. Further research, in the form of larger, highly powered RCTs will be needed to examine the efficacy of pharmacological and non-pharmacological interventions for patients with COVID-19-related olfactory dysfunction.

Author contributions

LJ conceived the idea and critically revised the article. All authors satisfied the ICMJE criteria for authorship. CP was the lead supervisor for the project.

Conflict of interest

CP reports grants from NIHR, ESPRC, and ENT UK, personal fees from Stryker, Abbott, and Olympus, outside the submitted work, and Trustee of Fifth Sense.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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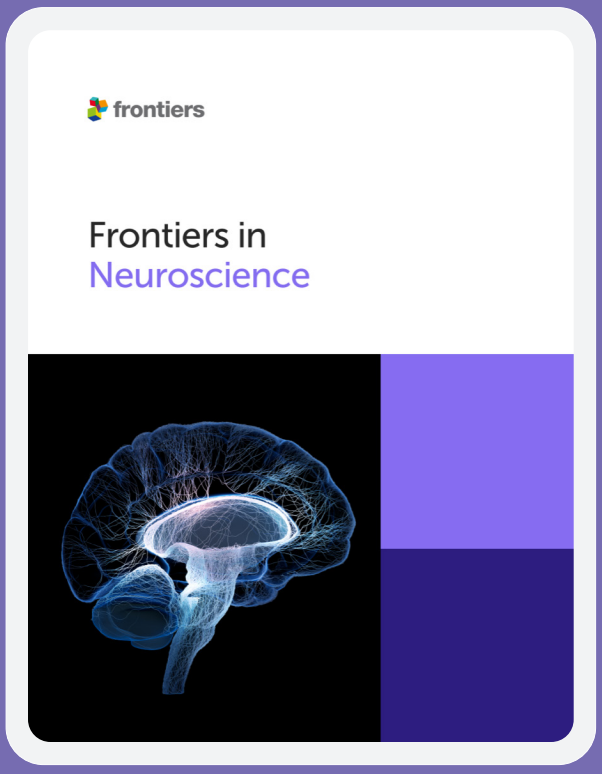

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