Title: Can Multisensory Olfactory Training Improve Olfactory Dysfunction caused by COVID-19?

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Keywords: Olfaction, Gustation, Vision, Multisensory, Olfactory Disorders, Olfactory Test, Quality of Life,

Manuscript Word count: 6513

Abstract

Background: Approximately 30-60% of people suffer from olfactory dysfunction (OD) such as hyposmia or anosmia after being diagnosed with COVID-19; 15-20% of these cases last beyond resolution. Previous studies have shown that olfactory training can be beneficial for patients affected by OD caused by viral infections of the upper respiratory tract.

Objective: The aim of the study is to evaluate whether a multisensory olfactory training involving simultaneously tasting and seeing congruent stimuli is more effective than the classical olfactory training.

Methods: We recruited 68 participants with persistent OD for 2 months or more after COVID-19 infection; they were divided into three groups. One group received olfactory training which involved smelling four odorants (strawberry, cheese, coffee, lemon; classical olfactory training). The other group received the same olfactory stimuli but presented retronasally (i.e., as droplets on their tongue); while simultaneous and congruent gustatory (i.e., sweet, salty, bitter, sour) and visual (corresponding images) stimuli were presented (multisensory olfactory training). The third group received odourless propylene glycol in four bottles (control group). Training was carried out twice daily for 12 weeks. We assessed olfactory function and olfactory specific quality of life before and after the intervention.

Results: The intervention groups showed a similar significant improvement of olfactory function, although there was no difference in the assessment of quality of life.

Conclusion: Both multisensory and classical training can be beneficial for OD following a viral infection, however only the classical olfactory training paradigm leads to an improvement that was significantly stronger than the control group.

Introduction

Acute infection with SARS-CoV-2 is associated with olfactory dysfunction (OD) such as hyposmia or anosmia (Karamali et al., 2022). Although the sense of smell recovers rather quickly in most participants (Jafar et al., 2021), long-term olfactory loss after COVID appears to be widespread. Depending on how this is assessed and the variant, percentages of chronic olfactory dysfunction, i.e., olfactory dysfunction that persists for more than 6 months after the infection seem to differ. For example, in the earlier studies this percentage ranged between 30% (Mazzoli et al., 2021) and 60% (Bussiere et al., 2022). However, in more recent Omicron variant the number of individuals with olfactory dysfunction was much lower ranging between 5% (Mella-Torres et al., 2022) and 17% (DeWitt et al., 2023).

Persistent olfactory dysfunction may have a heavy burden on the affected individuals. They have a higher risk of being exposed to hazardous situations such as fire, smoke, gas or spoiled food (Croy, Nordin, et al., 2014). Further, olfactory dysfunction affects eating and drinking (Yeomans, 2006), as well as social, sexual or work life (Bramerson et al., 2007). Thus, it comes as a no surprise that olfactory dysfunction is associated with higher rates of depression and anxiety (Kohli et al., 2016), eating disorders like bulimia or anorexia nervosa (Aschenbrenner et al., 2008), and, in the context of long-term COVID, with mood disturbances and cognitive impairment (Llana et al., 2023).

Currently, olfactory training is the intervention of choice for olfactory dysfunction following a viral infection of the upper respiratory tract (Hummel et al., 2009; Vance et al., 2023). During olfactory training, participants typically self-administer four odorants for twice a day for at least twelve weeks (Hummel et al., 2009). The exact underlying mechanism is unclear, but olfactory training may induce plasticity of the olfactory receptor neurons in the olfactory mucosa (Doty, 2019; Pieniak et al., 2022). Hence, olfactory training is also the therapy of choice for olfactory dysfunction following COVID-19 (Altundag et al., 2022; Bérubé et al., 2022; Le Bon et al., 2021; Pires et al., 2022).

In daily life, olfactory perception typically occurs in a multisensory context (Auvray & Spence, 2008). For example, when we eat an apple, we taste its sweetness and sourness, we smell its aroma via retronasal olfaction, we feel its texture; in addition, we see its color and hear the crunch while chewing (Croy, Hoffmann, et al., 2014) . In fact, flavor perception is the integration

of information from these individual sensory channels into one percept (Auvray & Spence, 2008), during which interactions occur between the single sensory channels (Small et al., 1997). Accordingly, multisensory stimulation and integration leads to changes in activation patterns in olfactory processing centers (Karunanayaka et al., 2015) with consequences on perception and behavior: for example, a congruent taste stimulus increases the intensity of retronasally presented odors (Green et al., 2012; Seo et al., 2013) and decreases detection thresholds (Dalton et al., 2000); together, they are integrated into more pleasant flavors (Fondberg et al., 2018). These effects are not limited to the chemical senses; for example, congruent visual stimuli enhance odor detection (Gottfried & Dolan, 2003), identification (Zellner et al., 1991) as well as color and shape related queues having an effect on visual performance and olfactory discrimination (Dematte et al., 2009; Jadauji et al., 2012).

Therefore, a multisensory olfactory training involving congruent gustatory and visual stimuli may have a superior effect compared to classical olfactory training with exclusively olfactory stimuli. We therefore hypothesized that the multisensory olfactory training could improve olfactory function like classical olfactory training in patients suffering from OD post-COVID-19.

Materials and methods

The protocol, its amendments and other documents were approved by the Medical Research Ethics Committee of the CIUSSS MCQ (MP-2021-486) and UQTR (CER-22-288-10.03).

Participants

We recruited 68 participants for the study, either via self-referral or by referral from other health professionals. Participants self-identified their genders. Our inclusion criteria were (1) being 18 years or older, (2) being a resident of Quebec, (3) suffering from olfactory dysfunction for 2 months or more after COVID 19. We excluded participants with (1) chronic rhinosinusitis, (2) pre-existing olfactory disorder before COVID-19, (3) nasal sinus surgery, (4) neurologic disorders such as Alzheimer or Parkinson's disease. We were able to follow up a total of 56 participants (41 women, 15 men, mean age = 42.9 (11.3) years).

INSERT FIGURE 1 HERE

Participants were assigned to two groups ((1) classical olfactory training - COT; (2) multisensory olfactory training – MOT at 1:1 ratio in a randomized manner, and no restrictions of groups were made. Randomization was carried out by a member of the research group who did not take part in the data collection process. Further, we included the data of a control group from an earlier study (Berube et al., 2022). In total, we recruited 23, 22 and 23 participants in the COT, MOT, and control group, respectively. Of them, we were able to follow up 20 (15 women, 5 men, mean age: 39.5 (9.6) years) participants in the COT group, 16 (11 women, 5 men, mean age: 46.3 (13.8) years) participants in the MOT group and 20 (15 women, 5 men, mean age: 43.5 (10.1) years) participants in the control group. The interval between onset of COVID-19 and the start of olfactory training was 269 (78) days, 346 (116) days and 246 (109) days in COT, MOT, and controls, respectively. The self-reported average interval between the diagnosis of COVID-19 and olfactory loss was 5.2 (S.D = 9.7) days.

Olfactory Training

Classical olfactory training: In the COT group, participants received an olfactory training kit consisting of amber opaque glass vials (30 ml, Fisherbrand Inc, USA), each of which contained (5 mL, soaked in cotton pads to prevent spilling) one of four different odors (strawberry, cheese, coffee, lemon; all food grade odorants from Foodarom Glanbia Nutritionals, St. Hubert, QC,

Canada). Each training session consisted in sniffing deeply each odorant for 10s, with 10s rest intervals between each odorant; we instructed participants to do this for a total of 5 minutes in line with (Hummel et al., 2009).

Multisensory olfactory training: In the MOT group, participants received an olfactory training kit consisting of the same four amber opaque glass vials (30 ml, Fisherbrand Inc, USA), but with a dropper lid. The bottles contained the same four odorants (20 ml) as in the classical olfactory training group. To this we also added corresponding tastants (sweet to the strawberry odorant; salty to the cheese odorant; bitter to the coffee odorant, sour to the lemon odorant). An overview of the used ingredients can be found in Table 1.

INSERT TABLE 1 HERE

For the MOT group, each training session consisted in placing a drop of a solution from a given bottle on the center of the tongue while simultaneously looking at a card with a corresponding picture for 15s followed by a 30s break. This procedure was repeated 4 times.

Control group: the control group received four identical looking bottles however these bottles were only filled with odorless propylene glycol. They followed the same procedure as the COT group and sniffed from the bottles. The data from the control group has been reported earlier (Berube et al., 2022).

Assessment of Olfactory Function

Olfactory function was assessed using the UPSIT (Doty et al., 1984). In short, the UPSIT is a scratch'n'sniff test that consists of identifying 40 microencapsulated odorants on paper booklets that are released upon scratching with 4 response choice per item. We recorded the number of correct responses out of 40 points. We further used the SQOD-NS (Mattos et al., 2019), an adapted version of the Questionnaire for Olfactory Dysfunction (QOD (Frasnelli & Hummel, 2005)), to assess the impact of olfactory dysfunction on daily life. The questionnaire comprises of 7 statements on the negative outcomes of olfactory dysfunctions that people suffer from.

Procedure

After randomization, participants were mailed a kit containing an olfactory training kit corresponding to their group along with two UPSIT. Upon reception of the kit, the research team set up a first video call with the participant. During this we carried out UPSIT and QOD.

Olfactory training was performed over a period of 12 weeks (Hummel et al., 2009) with participants self-administering the training twice a day. After six weeks, we called the participants by phone (1) to allow the participant to give us feedback about their olfactory function and (2) to verify and maintain compliance with the training procedure. In week 10, participants were contacted to schedule a meeting by the end of week 12. During the final meeting, UPSIT and QOD tests were performed again, and participants were debriefed.

Statistical Analysis

We used SPSS 29 (IBM Corp, Armonk, NY) for data analysis. We examined effects of *group* (intervention, placebo), *time* (before training, after training) on the dependent variables (1) olfactory function (UPSIT score) and (2) impact on daily life (QOD score) using a repeated measures ANOVA. We corrected post-hoc t-tests with the Bonferroni-Holm procedure to control for multiple comparisons. We carried out chi square tests to compare the number of participants who exhibited parosmia before and after the training. We set the alpha value at 0.05.

Results

Olfactory function:

Olfactory function (UPSIT scores) increased from 23.9 (5.6) points for COT, 23.1 (6.9) points for MOT and 23.9 (5.4) for controls before training to 29.2 (4.4) points, 26.2 (7.0) points and 24.9 (6.0) for COT, MOT, and controls, respectively, after training. The repeated measures ANOVA yielded a significant effect of *time* ($F(1, 53) = 19.4$, $p<.001$, Wilk's $\Lambda = .7$, partial $\eta2 = .27$) and a significant interaction *time* * *group*, ($F(2, 53) = 3.4$, $p = .3$, Wilk's $\Lambda = .09$, partial $\eta2 = .11$), but no effect of *group* ($F(2, 53) = 0.9$, $p = 0.4$).

To disentangle the interaction, we carried out 3 separate paired t-tests, one per group. While both the COT group ($t(19) = -3.834$, $p = 0.001$) and the MOT group ($t(15) = -2.357$, $p = 0.032$) showed significant improvement, there was no significant change in the control group ($t(19) = -1.021$, $p = 0.320$).

INSERT FIGURE 2 HERE

Impact on daily life:

Impact on daily life (QOD) scores before the training were 10.5 (4.9) points, 10.5 (3.3) points and 12.4 (4.6) points in COT, MOT, and control groups, respectively. After the training, these values were 9.4 (5.7) points, 9.7 (5.04) points and 11.0 (4.3) points for COT, MOT, and controls respectively. The repeated measures ANOVA yielded a significant main effect of *time* ($F(1, 53) = 6.9$, $p < .05$, Wilk's $\Lambda = 0.9$, partial $\eta2 = .11$), but no significant effect of *group* ($F(2,53) = 0.94$, $p = 0.4$) nor an interaction *time* * *group* ($F(2, 53) = 0.15$, $p = 0.9$, Wilk's $\Lambda = 1$, partial $\eta2 = .006$).

INSERT FIGURE 3 HERE

Parosmia

Before training, 18/20, 14/16 and 16/20 participants reported parosmia in COT, MOT, and controls, respectively. These numbers were 17/20, 15/16, and 19/20 after the training; there was no significant difference between groups ($X2(1, 56) = 0.23$, $p = 0.9$).

Discussion

Here we report the results of our study on the different protocols of olfactory training. Our main results are: (1) a 12-weeks training using both unimodal and multisensory (i.e., with congruent visual and gustatory stimuli) paradigm improved olfactory function in participants with persistent olfactory dysfunction after COVID-19 but not in the control group; (2) there was a significant improvement of impact on daily life scores in all groups.

This study shows that olfactory training helps to restore olfactory function in patients with OD following COVID-19, in line with earlier reports. In fact, olfactory training is effective in olfactory dysfunction due to upper respiratory tract infection (URTI) (Hummel et al., 2009; Hummel et al., 2017; Hura et al., 2020; Kattar et al., 2021; Konstantinidis et al., 2013; Ojha & Dixit, 2022; Patel, 2017). The exact mechanisms underlying recovery due to olfactory training are unknown. The regeneration of olfactory receptors in the epithelium has been put forward as a potential mechanism. Accordingly, both repeated exposure in rats (Wang et al., 1993; Youngentob & Kent, 1995) and olfactory training in humans (Hummel et al., 2018) increase electrophysiological signals from the olfactory epithelium. As a consequence, olfactory training increases olfactory bulb volume in both patients with olfactory dysfunction (Gellrich et al., 2018; Negoias et al., 2016; Rombaux et al., 2009) and healthy individuals (Filiz et al., 2022). It further improves different functional and morphometric measures including functional connectivity in the central chemosensory networks (Kollndorfer et al., 2015), as well as grey matter volume (Al Ain et al., 2019; Banks et al., 2016; Delon-Martin et al., 2013; Filiz et al., 2022) and activation levels (Chen et al., 2022) of olfactory processing areas. In an earlier study on a similar but different cohort (with the same control group), we used an olfactory training protocol (Bérubé et al., 2022). We observed an improvement of quality of life and subjective olfactory function, but no improvement on scores with a validated olfactory test. Again, together with the results of the present study, this suggests that the benefits of olfactory training in OD post-COVID-19 may be relatively limited.

While the effectiveness of olfactory training in olfactory dysfunction due to URTI is now well established (Hwang et al., 2023; Vance et al., 2023), researchers investigated several parameters to further improve its impact. These modifications include duration of the training, odor variety, odor intensity, pharmaceutical support, and other. For example, the use of steroids to support

olfactory training yielded mixed results, as one study showed additional benefit (Fleiner et al., 2012), while the others did not (Schepens et al., 2022). Other interventions such as the use of odorants of higher molecular weight (Poletti et al., 2017) and the use of odorants in higher concentrations (Damm et al., 2014) appear to be more promising. Increasing the number of odorants from four to eight (Pires et al., 2022) did not change the effectiveness of olfactory training, but changing odor sets during the training did (Altundag et al., 2015).

However, the parameter with the highest impact on appositive outcome of olfactory training appears to be the duration of the olfactory training protocol. For example, patients with olfactory dysfunction following COVID-19 who followed olfactory training more than 28 days showed greater long-term improvements compared to those who took the training less than 28 days (Denis et al., 2021). In the same line, 24-weeks olfactory training in patients with olfactory loss due to URTI showed significant improvements in olfactory identification and discrimination abilities after 3 and 6 months, but not after 1 month (Qiao et al., 2019). This is further supported, as olfactory training in patients with olfactory loss due to URTI yielded significantly better outcomes after 32 weeks (Geissler et al., 2014) and 56 weeks (Konstantinidis et al., 2016) when compared to 12 weeks. Even longer follow up periods (6, 12, and 18 months) lead to further improvement in patients with COVID-19 related olfactory dysfunction (Lechien et al., 2023). Protocols of such long duration may be more easily be carried out when stimuli are presented as drops onto the tongue rather than sniffing the headspace from bottles, and this is for two reasons. First, for individuals with olfactory dysfunction, it may be difficult to judge when an odor has evaporated from a bottle, while it is rather obvious when there is no more liquid in the bottle. Second, administrating odorants as drops onto to the tongue may help to reach olfactory stimuli of higher concentration, which is crucial for the positive outcome of olfactory training (Damm et al., 2014).

With long intervention periods, compliance with the training protocol becomes an issue (Vance et al., 2023). It is not surprising that extremely long training protocols to up to a year and a half are particularly useful in patients with strong adherence to the protocol (Lechien et al., 2023). Rendering olfactory training easier, e.g., using an olfactory ball, i.e., a ball containing 4 different holes to hold 4 different olfactory stimuli significantly increased adherence to the protocol and improved outcome (Saatci et al., 2020). Although we did not assess patient compliance, offering

multisensory stimuli for olfactory training may increase adherence; future studies should evaluate this potential.

In the present study, we integrated both visual and gustatory stimuli into the already existing olfactory training. Visual and olfactory stimuli have been combined for olfactory training before. For example, combining odors with digital images showed the largest clinically meaningful improvements in olfactory dysfunction due to COVID-19 (Denis et al., 2021; Khan et al., 2022). The underpinning to this is potentially that olfactory training leads to an increase in functional connectivity of the visual cortex with olfactory processing areas in patients with olfactory dysfunction due to URTI (Jiramongkolchai et al., 2021). In fact, the olfactory and the ventral visual processing streams converge in olfactory (e.g., orbitofrontal (Kuang & Zhang, 2014; Rolls, 2019; Rolls et al., 1996) or, piriform cortex (Qureshy et al., 2000)) and visual occipital cortex (Qureshy et al., 2000). Similarly to the olfactory-visual interactions, olfaction and gustation senses influence each other mutually (Czarnecki & Fontanini, 2019) by having shared stimuli (e.g., food) and converging central pathways in the orbitofrontal cortex (Czarnecki & Fontanini, 2019; Rolls, 2016) and insula (Mazzola et al., 2017).

In this study, we did not find any superiority of a multisensory training paradigm over a classical olfactory protocol. While potentially this may be due to the small sample size, it also suggests that there is no major advantage of multisensory of olfactory paradigm. However, several studies show the benefits of multisensory training over using unimodal sensory training on a series of diverse tasks such as audio-visual integration (Seitz et al., 2006; von Kriegstein & Giraud, 2006), postural stability (Hu & Woollacott, 1994), dyslexia (Kast et al., 2007) and auditory impairments restored with cochlear implants (Isaiah et al., 2014). While such a superiority of multisensory training is not evident in our study, one could imagine a scenario in which multisensory stimuli (e.g., candies) could be associated with higher compliance than pure olfactory training. This should be investigated in future studies.

This study has some limitations. First, we included a relatively small sample yielding limited statistical power. Second, in all groups we recruited more women than men. While this may reflect gender-related differences in the impact of COVID-19 on olfactory abilities (Bussiere et al., 2021) in line with other URTI studies (Liu et al., 2016; Sorokowski et al., 2019), it could potentially skew our results as women typically score higher in olfactory identification and

memory tasks (Doty & Cameron, 2009). Third, participants self-administered the training, hence it is not possible to know with certainty if participants actually followed the suggested routine as recall bias or social desirability might have affected the results (Vance et al., 2023). It is therefore important to put adherence rules or tasks in place to track this data such as keeping journals or reports (Vance et al., 2023). Fourth, this study was carried out during the pandemic with restrictions in place to test participants hence the testing was done remotely via zoom, this led to a limiting testing option for the research team. Fifth, as mentioned previously, we do not know if participants complied with the process accurately or on time every day. Compliance issue could be addressed in further studies with compliance sheets or alternative methods of testing since now the pandemic restrictions have been lifted.

In conclusion, we show that both a multisensory olfactory training and a classical olfactory training can lead to improved olfactory function in participants with chronic olfactory dysfunction following COVID-19.

Acknowledgments

Ethical statement and funding resources

This study is funded by NSERC, Fonds de Recherche du Québec – Santé (FRQS), Fondation Santé Trois-Rivières (CIUSSS – MCQ). We do not have any conflict of interest to declare.

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Figure Legends

Figure 1. Number of participants at each step of the study.

Figure 2. Olfactory test (UPSIT) scores before and after the training for (1) a group following a classical olfactory training protocol, (2) a group following a multisensory olfactory training protocol, and (3) a control group. The asterisks denote a significant difference in smell test scores before and after the training.

Figure 3. Impact on daily life (Questionnaire of Olfactory Disorders) scores before and after the training for (1) a group following a classical olfactory training protocol, (2) a group following a multisensory olfactory training protocol, and (3) a control group.

Table

Flavor	Odorant Product#	Odorant Volume	Tastant Product#	Tastant Manufacturer	Tastant amount
Strawberry	Strawberry MET0003559	0.02ml	Sucrose #424500010	Thermo Fisher, St Laurent, QC	0.4mg
Cheese	Cheese MET0017403	0.2ml	Sodium Chloride #127038.119541	BDH Inc. LOT, Toronto, ON	0.08mg
Coffee	Coffee MET0017403	0.2ml	Sucrose octaacetate #W303801	Sigma Aldrich, Oakville, ON	0.008mg
Lemon	Lemon MET0000055	0.2ml	Citric acid #X000HT86Q5	Milliard Brands, Lakewood, NJ	0.3mg

Table 1. Table shows the odorants and tastants used for multisensory stimulation. Odorants are all from Foodarom, St Hubert, QC. Odorants and tastants were dissolved in 20 mL of demineralized water.