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# Designing novel "Smell-Aids" to improve olfactory function in post COVID-19 era

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## Abstract

**Background** Eyeglasses, hearing aids, etc., all serve to enhance the sensory stimuli to enable patients to see or hear things that they would not otherwise be able to, but we have no equivalent technology for olfaction, a pressing issue in the post-COVID era.

**Methods** We attempt to invent "Smell-Aids" by non-invasively enhancing intranasal odorant delivery to the olfactory epithelium, using two prototypes: (a) a nasal foam plug with a diagonal channel embedded to direct air/odor flow upwards to the olfactory region; (b) a clip (similar to what synchronized swimmers use) pinching a critical nasal valve region that may intensify the nasal airflow vortex to the olfactory region.

**Results** We first tested these prototypes in counter-balanced orders on 58 healthy subjects, where their measured odor detection thresholds to phenylethyl alcohol significantly improved with both prototypes in subjects with normal smell function (baseline: 8–16.5, $n=30$, $12.49 \pm 2.8$, plug: $14.42 \pm 4.9$, pinch: $14.73 \pm 5.4$, $p<0.05$), but not in subjects with "super" sensitivity at baseline (> 16.5, $n=28$). Next, we tested the prototypes on 54 patients with confirmed olfactory losses (age 21–80 years, median 54.5), the majority of whom (37/54 = 69%) were post-COVID long haulers (infected 12/15/2019 to 10/4/23; persisted 30 to 1260 days, median 22 months). The remaining non-COVID smell losses ($n=17$) span significantly longer from 5 months to 27 years (median 8.5 years). The 9-item NIH toolbox odor identification score significantly improved after application of both smell aids (baseline: $4.30 \pm 2.27$, plug $5.11 \pm 2.32$, pinch $4.82 \pm 2.06$, mixed model $p<0.05$), especially among the non-COVID cohort. For COVID long haulers, only the nasal plug remained effective ($p<0.05$). Subgroup analysis was performed on patients who reported diminished (hyposmia/anosmia 38/54) vs distorted smell (parosmia/phantosmia 27/54, $n=11$ reported both) and showed that the nasal plug remains effective for both cohorts ($p<0.05$) while the pinch is only effective for the hypo/anosmia cohort ($p<0.05$).

**Conclusions** These results preliminarily demonstrated the novelty of improving olfactory function through different peripheral mechanisms for different patient and normative cohorts and may one day lead to an effective over-the-counter smell aid.

**One-sentence summary** Enhancing olfactory functions in healthy and patient cohorts through improving intranasal air and odorant delivery.

**Trial registration** ClinicalTrials.gov NCT05920330.

**Keywords** Olfactory dysfunction, Post-acute sequelae of SARS-CoV-2, PASC, Long COVID, Chronic COVID

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## Background

Throughout human civilization, innovations to enhance our sensory functions through peripheral mechanisms were important thrusts to the advancement of humanity, e.g., for vision: the invention of the microscope by Hooke in 1665, Galilei's telescope in 1609, and eyeglasses around the tenth century; for hearing: the stethoscope by Laennec 1816, hearing aids around 1895—they all serve to enhance the external stimuli to enable us to see or hear things that we wouldn't otherwise be able to, in both healthy and disease states. But we have no equivalent technology for the sense of smell—enhancing the external odor signal.[3–6]. Olfaction plays a vital role in our daily lives, helping us detecting environmental dangers such as smoke or spoiled food, enhancing the enjoyment of fragrances and cuisine, and fostering social bonds (e.g., between infants and parents) [1]. Olfactory losses, which have a significant health impact, can result from various factors, including chronic sinusitis or nasal inflammation, head trauma, neurological diseases (such as Alzheimer's disease and Parkinson's disease), congenital conditions, exposure to toxic chemicals or pollutants, and aging [2]. In recent years, COVID-19 emerged as another major cause of olfactory dysfunction, making these sensory losses a hallmark symptom of COVID-19 infection [3–6]. Meta-analyses of published studies before the omicron variant indicate that over 50% of COVID-19 patients self-reported smell loss [7, 8]; this increases to 86% in studies using validated psychophysical measurements [9, 10]. Most importantly, in approximately 15% of COVID-19 patients, smell loss persisted over months, even years (long COVID) [11, 12]. These patients also self-report much higher incidence (7–11%) of parosmia (distorted odor perception) or phantosmia (olfactory hallucination, usually foul, in the absence of odorant) [5, 13] than do typical viral infection patients [14]. More than 50% of the parosmia and phantosmia cases persisted over 90 days, a different time profile than for hyposmia and anosmia cases [5, 13]. Unfortunately, there currently are no effective targeted therapies for persistent olfactory dysfunction, with most being supportive or experimental (e.g. olfactory training and platelet-rich plasma) [15, 16]

The sense of smell starts with inhaling or sniffing volatile chemical molecules through airflow to the olfactory epithelium, which is confined to a remote and small region in the superior human nasal cavity [17]. A sufficient amount of odorant delivered from the ambient environment to the olfactory epithelium is likely a critical prerequisite for normal olfactory function [18]. Yet, less than 15% of the air inhaled during a normal breath reaches the olfactory epithelium [19–22]. One would propose that we can potentially enhance the amount of nasal airflow to the olfactory region to improve olfactory functions. This may be an effective approach for patients with nasal obstruction and insufficient airflow to the olfaction region to begin with, but could extend to patients with sensorineural causes of smell losses, such as post-COVID-19. Analogously, hearing aids serve as crucial therapeutic and symptom management devices for individuals with conductive and/or sensorineural hearing losses [23]. However, no noninvasive technique currently exists to achieve that for olfaction. One reason is that the impact of the complex nasal cavity anatomy on nasal airflow is relatively unclear, and the degree of variation in olfactory acuity that the conductive factors can account for has not been entirely determined [24–26]. Previously, research using computational fluid dynamics (CFD) modeling showed that airflow travels along the path of least resistance and is easily redistributed if one path is altered; and depending on the location, relatively minor changes in key nasal regions may dramatically alter airflow distribution and significantly impact the ability of odorant molecules to reach the olfactory epithelium without affecting total nasal airflow rate [27–29].

To fill this gap, in this report, we attempt to design a "Smell-Aid" using two creative inventions: (1) a nasal foam plug with a diagonally embedded air channel that, based on our CFD simulation, would direct more odorant delivery to the olfactory region; (2) a nasal clip modifying the key nasal region identified in previous CFD studies that may intensify the nasal airflow vortex towards the olfactory region. We then tested the efficacy of such designs among healthy controls with varying baseline olfactory sensitivities as well as among patients with confirmed olfactory losses of broad etiologies, including COVID-19-related losses.

## Methods

### Smell aids designs

Our 1st invention is a novel "nasal plug" made from foam ear plugs (classic soft™, 311–6000, 3M, Saint Paul, MN) with a plastic straw, 5 mm in diameter (purchased from local supermarket), manually embedded in a diagonal direction (~ 30°). Once inserted into the nostril, the foam plug can be rotated freely to re-route nasal airflow in different directions. We first performed a CFD simulation based on a previously published 3D numerical nasal model of healthy control [30] to confirm whether the nasal plug can effectively redirect airflow to different targeted nasal regions (as shown in Fig. 1). In brief, the anterior 2 cm (the length of the foam plug) of the nasal vestibular is blocked off, with an air channel of 5 mm in diameter 30° diagonal from the center line is virtually created in two directions (up or down). Next, inspiratory quasi-steady laminar [20, 27] nasal airflow was simulated as previously described and validated [30, 31]

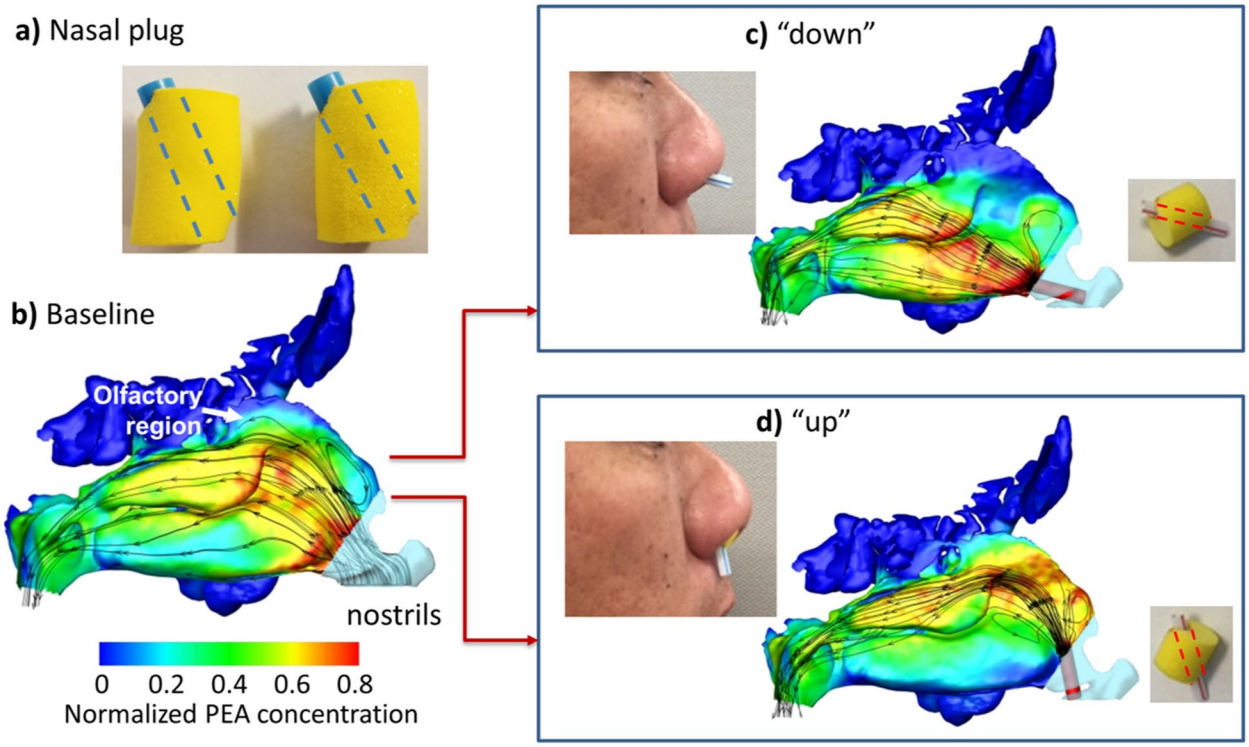


**Fig. 1** The design of a nasal foam plug to direct odorant delivery to the olfactory region. **a** A novel nasal foam plug with a straw, 0.5 mm in diameter, embedded diagonally. **b** Nasal airflow pattern (black lines) simulated by computational fluid dynamics (CFD) modeling of one healthy control, with color code showing normalized absorbed odor concentration on the nasal mucosa when the subject inhales 100 ppm of phenyl ethyl Alcohol (PEA). The nasal plug inserted into the nostrils in different orientations to redirect the airflow toward **c** the inferior turbinate region and **d** toward the olfactory region

on the modified nasal models. A physiologically realistic pressure drop of 15 Pa between the nostrils and the nasal pharynx is prescribed for restful breathing [27].

The simulation results are shown in Fig. 1, where the color code is the normalized absorbed odor concentration on the nasal mucosa when the subject inhales 100 ppm of phenyl ethyl Alcohol (PEA, a common rose-like odorant). With the downward orientation, airflow is directed downward towards the inferior turbinate. With the upward orientation, airflow is directed superiorly, with significantly higher odor concentrations delivered to the olfactory region. This confirmed that the different nasal plug orientations are capable of re-directing airflow to different airway regions, including the olfactory region, compared to the baseline.

Our second invention is inspired by a previous study examining the effect of normative variations of nasal anatomy and airflow on olfactory function [30]. The rationale for that study was that it is well established that human olfactory acuity has significant normative variability; we ask whether the normative variations in internal nasal anatomy and aerodynamics could account for any portion of that variation. Healthy volunteers ($n=22$) underwent CT scans for CFD modeling of nasal airflow patterns. Unilateral odor detection thresholds (ODTs) for PEA, l-carvone, and d-limonene (from high to low mucosal solubility) were measured ($n=44$ sides). The most prominent observed normative variations in nasal aerodynamics was the forming of an anterior-dorsal airflow vortex in some but not all nasal airways (Fig. 2a), with the vortex size (D normalized by the nasal cavity length [L]) significantly correlated with the measured odor detection thresholds (ODT) of l-carvone (mint odor, $r=0.31$, $p<0.05$). The formation of the vortex is likely the result of the narrowing of the anterior upper nasal vestibule cartilage region (Fig. 2b)—called the "notch" [32]. The degree of the notch, indexed as the ratio of notch depth and nasal cavity length (Notch Index = h/L), significantly correlates with vortex size ($r=0.76$, $p<0.001$) as well as with the ODT for PEA ($r=0.32$, $p<0.05$) and l-carvone ($r=0.33$, $p<0.05$). The ODT of d-limonene, a low-mucosa-soluble odor, did not correlate with any of the anatomical or aerodynamic variables. Nasal resistance also did not correlate with any ODTs. The study revealed that a specific narrowing of the vestibule

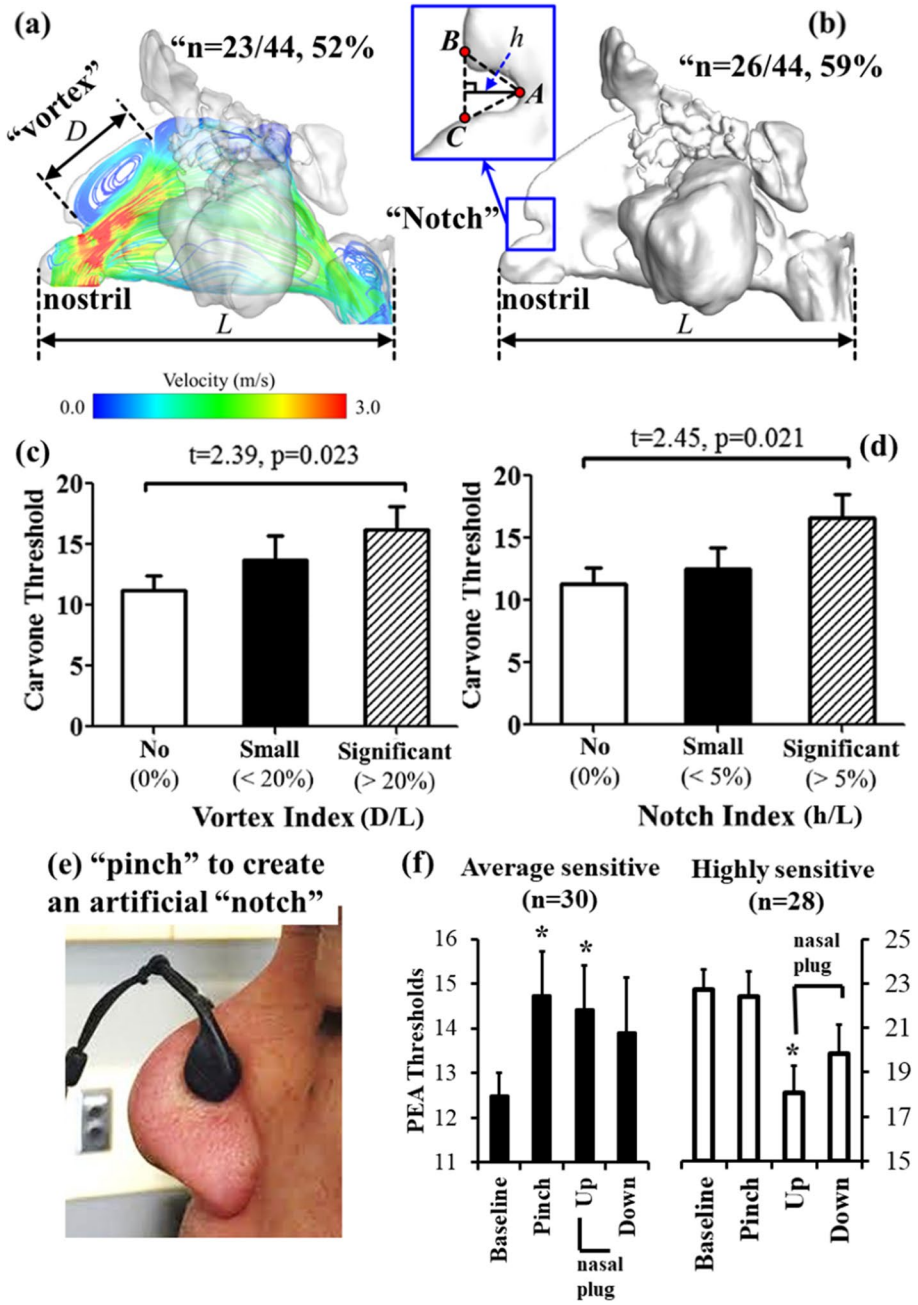


**Fig. 2** A nasal clip modifying the key nasal region that may intensify the nasal airflow vortex towards the olfactory region. **a**, **b** Variation of anterior nasal airflow vortex in some but not all healthy controls (**a**), which is linked to a nasal vestibule narrowing—"notch" (**b**). **c**, **d** A narrower vestibule region (high "notch") likely intensifies the airflow vortex toward the olfactory region, leading to better olfactory sensitivity to l-carvone. **(e, f)**. A nasal clip pinches the nose to create an artificial notch (**e**) that, along with "nasal plug upwards," both significantly improve olfactory sensitivity (**f**) for subjects with moderate baseline PEA detection thresholds (8–16.5) but not for those highly sensitive (> 16.5), and not in the control condition—nasal plug, "downward"

region (notch) intensifies an airflow vortex toward the olfactory region and may result in better olfactory sensitivity. A flash of idea emerges: can we use a nasal clip (similar to what synchronized swimmers use, item #786,398, REI.com, Recreational Equipment, Inc.)) to partially pinch an artificial notch without completely blocking the nose (Fig. 2e)—would that intensify the airflow vortex to the olfactory region and improve subjects' olfactory performance? When applying the nasal clip, the force and degree of the "pinch" is adjusted to

not create pain and not completely block the nasal airway so that the subjects can still breathe freely.

### Subjects

We tested whether or not one or both of these inventions can enhance the olfactory sensitivity as a "smell aid" in analogy to hearing aids or eyeglasses that amplify peripheral sensory stimuli, first on 58 healthy controls, recruited from the local community (Columbus, OH) through website ads and flyers. Their age range is 22 to 72 years old with a median of 25, and consists of 30 male, 28 female, 50 Caucasian, 1 Hispanic Caucasian, 4 Asian, and 3 African American.

We then tested the "smell aids" on 54 patients with olfactory losses (age 21-80y, median 54.5, male, 18, female, 36), recruited through local ads and ads to the patient advocate group. We included patients with all causes of smell losses, except congenital olfactory losses. Majority of these patients (37/54 = 69%) reported their smell losses being COVID-19 related (infected 12/15/2019 to 10/4/23) with the diagnosis to testing time gap 30 to 1260 days (median 22 months)—potential "Long Hauler." Most ($n = 28/33$ with $n = 4$ did not provide the information) were not fully vaccinated prior to testing positive for COVID-19. 11/37 had reported 2 or more instances of COVID diagnosis. Only 1/37 was hospitalized for COVID; as such, they were considered mostly mild cases by CDC standards. The non-COVID smell losses ($n = 17$) span from 5 months to 27 years (median 8.5 years), significantly longer than COVID-19-related patients ($T$-test, $p < 0.001$). Causes of these patients' smell losses vary: 6 related to head trauma, 3 from head neck cancer and surgery, 1 due to nasal polyps, and 7 reported unknown causes. Out of these 54 patients, 38 reported a diminished sense of smell (hyposmia/anosmia), while 27 reported a distorted sense of smell (i.e. parosmia and/or phantosmia), with $n = 11$ reported both. 21/37 COVID participants reported diminished smell and 25 with distortion. All 17 non-COVID-related participants reported diminished smell, with 2 also reporting distortion.

### Smell tests

For healthy controls, ODTs for PEA were measured in one session (same day) in counterbalanced order at baseline (without any smell aids), with a nasal clip and with the nasal plug inserted in up and down directions (baseline is included in the counter-balanced ordering). ODTs are obtained by using an objective, two-alternative, forced-choice, and modified stair-case method that has been previously described [2]. The odorant PEA is diluted into mineral oil in a 29-step semi-log dilution series, starting with a concentration of 100% v/v. 10 ml of each dilution is placed into a clean, 400 ml plastic squeeze bottle fitted with a flip-top cap. At each trial, the subject squeezes and sniffs from two bottles sequentially, containing either blank (only the solvent) or the appropriate dilution step of the odorant in a counter-balance order, and is forced to make an identification of which one contains the odorants. An incorrect response leads to a 1-dilution-step increase in concentration on the next trial, whereas two successive correct responses lead to a 1-dilution-step decrease. A reversal is considered to have occurred at points where the concentration sequence changes from decreasing to increasing (negative reversal) or increasing to decreasing (positive reversal). The procedure is terminated after five reversals, and the threshold is calculated as the mean of the dilution-step values of the five reversals. According to the previously established clinical criteria for diagnosing olfactory disorders [2], the normal range for the PEA threshold is $\geq 8$ dilution steps.

For the patients, the NIH toolbox odor Identification (ID) test includes 9 scratch and sniff odor ID cards, which were measured and recorded utilizing a Qualtrics survey. The subject is asked to scratch and sniff each of the 9 cards in random order, and select the odor identity based on 4 multiple choices. All tests were conducted within one test session either in person (35/54) or supervised via Zoom (19/54).

### Statistical method

Linear mixed model (SAS Enterprise v9.4) was used to examine the changes of detection thresholds or odor identification scores between baseline and different manipulations (pinch, nasal plug) with random intercepts for each participant. All subjects completed baseline and nasal pinch testing; however, 14 out of 58 healthy controls did not complete nasal plug "up" testing, and 22 healthy controls did not complete nasal plug "down" testing due to time-consuming threshold testing. All patient cohorts completed all 4 conditions in counter-balanced order. Linear mixed model is well suited to handle such missing data situations and adjust for confounding factors (age, gender, testing order). The detailed result is shown in Table 1.

## Results

### Healthy controls

Examining the ODTs for PEA measured at baseline, with a "pinch" and the nasal plug inserted in up and down directions, first, we observed a statistically significant correlation between the degree of ODT improvement and baseline olfactory sensitivity (Pearson $r = -0.36$, $p < 0.05$), with larger improvement in subjects with less sensitive baseline smell function. This makes sense—as an analogy, corrective lenses may significantly improve suboptimal vision but only have a limited effect on a

**Table 1** Linear mixed model examined the changes of smell test scores between baseline and different manipulations (pinch, nasal plug) for both healthy control and patients

| (a) Healthy control linear mixed model (adjusted for age, gender, testing orders) | | | | | |
|---|---|---|---|---|---|
| PEA baseline categories | Difference with baseline | | 95% confidence | | *p*-value |
| | | Estimate | Lower | Upper | |
| 1: "Normal" smeller ≤ Median(16.4) (*N* = 30) | "pinch" vs. baseline | 2.066 | 0.334 | 3.797 | 0.021* |
| | Nasal plug "down" vs. baseline | 1.366 | −0.641 | 3.372 | 0.171 |
| | Nasal plug "up" vs. baseline | 1.667 | 0.092 | 3.242 | 0.039* |
| 2: "super" smeller > Median (16.4) (*N* = 28) | "pinch" vs. baseline | −0.329 | −1.722 | 1.065 | 0.633 |
| | Nasal plug "down" vs. baseline | −0.903 | −3.426 | 1.621 | 0.463 |
| | Nasal plug "up" vs. baseline | −2.630 | −4.697 | −0.563 | 0.015* |
| (b) Patients with smell losses linear mixed model (adjusted for age, gender, testing orders) | | | | | |
| Patient cohorts | Difference with baseline | | 95% confidence | | *p*-value |
| | | Estimate | Lower | Upper | |
| All patients (*N* = 54) | "pinch" vs. baseline | 0.542 | 0.135 | 0.949 | 0.009* |
| | Nasal plug "down" vs. baseline | 0.673 | 0.258 | 1.088 | 0.002* |
| | Nasal plug "up" vs. baseline | 0.805 | 0.394 | 1.216 | < 0.001* |
| COVID patients (*N* = 37) | "pinch" vs. baseline | 0.325 | −0.136 | 0.786 | 0.165 |
| | Nasal plug "down" vs. baseline | 0.446 | −0.035 | 0.926 | 0.069 |
| | Nasal plug "up" vs. baseline | 0.691 | 0.217 | 1.165 | 0.005* |
| Non-COVID patients (*N* = 17) | "pinch" vs. baseline | 1.065 | 0.190 | 1.940 | 0.018* |
| | Nasal plug "down" vs. baseline | 1.076 | 0.217 | 1.935 | 0.015* |
| | Nasal plug "up" vs. baseline | 0.938 | 0.071 | 1.805 | 0.035* |
| Hypo/anosmia patients (*N* = 38) | "pinch" vs. baseline | 0.661 | 0.164 | 1.158 | 0.010* |
| | Nasal plug "down" vs. baseline | 0.891 | 0.375 | 1.407 | < 0.001* |
| | Nasal plug "up" vs. baseline | 0.927 | 0.417 | 1.436 | < 0.001* |
| Paro/phantosmia Patients (*N* = 27) | "pinch" vs. baseline | 0.460 | −0.088 | 1.008 | 0.098 |
| | Nasal plug "down" vs. baseline | 0.401 | −0.155 | 0.957 | 0.155 |
| | Nasal plug "up" vs. baseline | 0.836 | 0.273 | 1.398 | 0.004* |

* indicating significant ($p < 0.05$)

perfect 20/20 vision. To confirm this observation, we divide our sample based on the median of baseline PEA thresholds (=16.5) into "normal" [2] (PEA 8–16.5, $n = 30$) and "super smeller" (PEA > 16.5, $n = 28$) groups. The improvement in PEA thresholds was significant for both nasal pinch and "nasal plug upwards" condition in the normal sensitivity group (baseline 12.49 ± 2.8, pinch 14.73 ± 5.44, upwards 14.42 ± 4.87, $p < 0.05$, Fig. 2f, linear mixed model adjusted for age, gender and test order, see Table 1), but unfortunately not among "super smeller" group, nor in the control condition—nasal plug "downward" (13.9 ± 5.23, $p > 0.05$).

### Patients with olfactory losses

Next, we tested the "smell aids" on 54 patients who self-reported olfactory losses. All participants' olfactory losses were subsequently confirmed with the 9-item NIH toolbox odor ID score based on age and gender-adjusted normative cutoffs [33, 34]. After the application of both smell aids in counterbalanced order, we observed their odor ID score significantly improved (baseline: 4.30 ± 2.27, pinch 4.82 ± 2.06, plug 5.11 ± 2.32, mixed model $p < 0.05$, see Fig. 3 and Table 1), especially among the non-COVID cohort. For COVID long haulers, only the nasal plug showed significant improvement ($p < 0.05$). Significant subgroup differences were observed among different smell loss cohorts: odor ID scores among non-COVID patients were significantly lower than that of long-COVID patients at baseline, and odor ID scores among patients who reported diminished smell (hyposmia/anosmia 38/54) were significantly lower than that of patients who reported distorted smell (parosmia/phantosmia 27/54, $n = 11$ reported both). The incidents of smell distortion were much higher in the COVID-19 cohort (25/37), while all 17 non-COVID patients reported diminished smell, with only 2 also reporting smell distortions. Smaller portion of the COVID cohort (21/37) reported diminished smell. Further subgroup analysis showed that the nasal plug upwards remains effective for all cohorts, while the pinch is only effective for the hypo/anosmia and non-COVID cohorts.

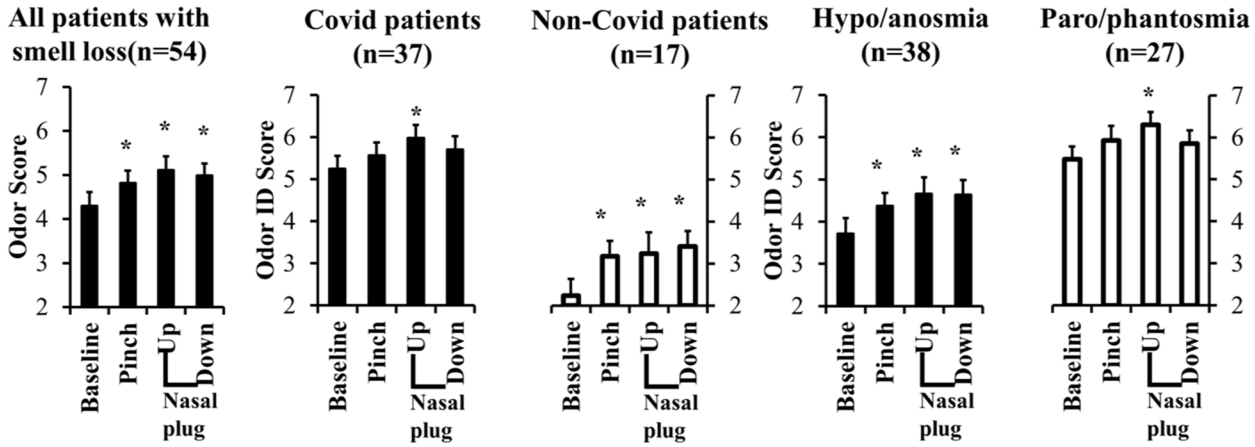


**Fig. 3** Test prototypes of smell aids in counter-balanced order on 54 patients with confirmed olfactory losses. Majority (37/54 = 69%) were post-COVID long haulers. The 9-item NIH toolbox odor ID score significantly improved after the application of both smell aids, especially among the non-COVID cohort. For COVID long haulers, only the nasal plug showed significant improvement ($p < 0.05$). Subgroup analysis was performed on patients who reported diminished (hyposmia/anosmia 38/54) vs distorted smell (parosmia/phantosmia 27/54, $n = 11$ reported both) and showed that the nasal plug remains effective for both cohorts ($p < 0.05$) while the pinch is only effective for the hypo/anosmia cohort ($p < 0.05$)

## Discussion

A canonical principle of olfaction, regardless of terrestrial vertebrates, crustaceans, or insects, is that odorant molecules must be transported through airflow prior to their chemospecific binding to the receptors expressed on olfactory receptor neurons. Active sampling serves to improve olfactory functions by enhancing such transport processes that can take many forms across species, e.g., respiratory sniffing by terrestrial vertebrates, antennule flicking by crustaceans, or surging and casting by flying insects [35]. For humans, sniffing represents active sampling to likely improve olfactory function [36]. In particular, we sniff much stronger and vigorously to detect a weak odor, so a common assumption is that stronger airflow during inhalation (sniffing) may benefit olfactory sensitivity. But we often overlook the fact that due to the protective location of the human olfactory epithelium, only a small portion of inhaled air can reach there. So, potentially, modulating the distributions of the intranasal airflow can be more effective than increasing the overall airflow; however, until now, we have no effective way to test that.

Both the "nasal plug" and "pinch" represent simple and innovative ways to modulate the intranasal airflow. They are counterintuitive in a way, as both manipulations likely increase the nasal resistance and potentially limit the total nasal airflow rate during sniffing. Therefore, their effectiveness is a test of whether modulating the distributions of the intranasal airflow can be an effective approach to designing a smell aid. Previous evidence did show that in some conditions, sniffing longer rather than stronger that may improve olfactory function, especially in nostrils with higher nasal resistance [37], and that human sniffing volume and duration can be rapidly modulated in an odorant-dependent fashion through the olfactory-motor interaction [38]. This potentially represents an adaptive tradeoff between increasing the total airflow rate and accumulating more odor molecules over time in the olfactory region. During the "nasal plug" and "pinch" manipulations, all subjects are allowed to freely "sniff," so they may retain such behavior adaptation under the increased nasal resistance. This might be the reason that some patient cohorts (e.g., non-COVID smell loss) improved olfactory function in the control condition: the nasal plug-down orientation. However, the increase in nasal resistance cannot be the only factor, as nasal plug-up orientation is more effective in patient and normative cohorts than the down orientation, where the increase in nasal resistance is essentially the same as the nasal plug-up orientation, but without the benefit of airflow redirection. Thus, optimal improvement in olfactory sensitivity should be due to both enhancement of intranasal airflow to the olfactory region, as we hypothesized, in addition to the potential effect of increased nasal resistance and motor-control of overall flow rate when the "nasal plug" and "pinch" were applied.

The effectiveness of the two prototypes of smell aids varies across different subject cohorts. For example, the "pinch" is likely more effective in the normative cohorts, whose olfactory sensitivity varies significantly. Even with the odor stimuli prepared with 29 semi-log dilution steps, 5 of the healthy subjects still bottom out (able to

detect the lowest concentration) that is over 10 orders of magnitude higher in concentration than the normative cutoff (>=8). This is partly why different olfactory tests are used for different cohorts. Odor ID tests for patient groups are suprathreshold that the normative cohort may perform perfectly even at baseline, incapable of observing any improvement. For instance, the normative range for a 40-year-old male is 8 or above, allowing for at most a 1-point increase before hitting the ceiling (9). In contrast, detection threshold tests operate at peri- or subthreshold levels and have a broader normative range of 8 to > 30. However, these tests can be too difficult and time-consuming for patient cohorts to complete repeatedly. Nevertheless, why some normative subjects have such remarkable olfactory sensitivity itself is an interesting question—perhaps those subjects with super sensitive olfaction have a perfect nasal structure, in addition to extremely high neural sensitivity that any disruption to their natural state, e.g., adding additional nasal resistance with the plug, would lead to decreased olfactory sensitivity. Indeed, the data do suggest that the nasal plug, regardless of orientation, resulted in worse olfactory sensitivity among the "super smeller" group, although the nasal pinch's negative impact is much less. So, potentially, in the future, we can design different "smell aids" based on different manipulations that can be applied to different populations with varying baseline olfactory sensitivities.

The effectiveness of smell aids on COVID-19-related olfactory losses is perplexing, as this type of loss likely involves inflammatory damage to sensorineural components rather than an obstructed nasal passage. We hypothesize that simply improving odor stimulus delivery may provide some symptomatic relief even for sensorineural losses. Using hearing aids as an analogy, they are the first-line treatment option even for individuals with sensorineural hearing loss, where damage may involve hair cells, auditory nerves, or central pathways. Despite that the conductive pathway is not the primary issue, hearing or smell aids may still effectively improve sensory perception by amplifying the stimuli. Similarly, another puzzling observation is the effectiveness of smell aids in patients with parosmia or phantosmia, where the dysfunction lies not in the ability to detect odors but rather in the distorted perception of odors or even clean air. Our data indicate that these patients generally have higher (better) baseline odor identification scores and show less improvement with our intervention. Notably, only the nasal plug in the "up" direction led to statistically significant improvement. During the tests, many patients expressed sentiments such as, "I think this odor is coffee, but it doesn't smell at all like the coffee I used to know. However, I recognize now that it is coffee." This suggests that while their odor identification is technically correct, it does not fully capture their dysfunction and the challenges they experience. To our knowledge, few objective olfactory tests currently exist that effectively assess parosmia or phantosmia beyond subjective self-reporting. Nevertheless, we hypothesized that even in such cases, increasing odor delivery may help the patients to process and recognize altered odor information more effectively. These remain areas in need of further research and refinement.

While we presented some interesting preliminary results, many questions remain to be examined. First, is a particular baseline nasal anatomy required for a greater effect? For example, whether someone without a preexisting nasal notch may benefit more from the pinch than someone with a preexisting nasal notch? We do not know yet. We observed that the pinch improvement significantly correlates with nasal plug improvement (healthy: Pearson $r=0.33$, $p<0.05$; patients: $r=0.639$, $p<0.001$). Potentially, the pre-existence of the notch may also affect the outcome of the nasal plug, making it easier or more difficult to redirect the airflow, leading to their significant correlation. Secondly, our previous study suggested that the sorptive properties of the odors would make them more or less susceptible to airflow distribution changes [27, 30]. Due to time constraints, we only tested the "aids" using one highly soluble odor (PEA), while the odor ID test contains complex odors often with a mixture of odorants with varying sorptive properties. It remains to be examined whether the varying effectiveness of "smell aid" is due to the range of odorants with diverse solubility as well as other physiochemical factors. Hypothetically, the nasal plug might be less influenced by the sorptive effect since it provides a more direct enhancing of odor delivery to the olfactory region, rather than relying on intensifying air circulation ("pinch"), and we did observe that the "pinch" technique was slightly less effective in enhancing odor ID, possibly because the complex odors used. This hypothesis awaits future investigation. In the future, we can use CFD modeling to predict if one of these manipulations can enhance airflow and odor sorption to the olfactory region based on individual anatomy and the odorants' physical properties and then correlate the prediction to the subject's olfactory measurements.

One potential limitation of the study is the small effective size, which is 1.6 ~ 2 dilution steps in ODT for healthy and 0.5 ~ 1 out of 0–9 odor ID score for patients (see Table 1), but that is comparable to the current best available options. For example, a meta-analysis of olfactory training, one of the go-to supportive treatments for olfactory dysfunction, showed an effect of 3.77 (95% confidence interval [CI], 2.28 to 5.26) in TDI score, which consists of 3 components, each 0–16 score for a total of

48 points [39]. Its treatment effect in the odor ID component is 1.61 (95% CI, 0.55 to 2.68) out of a total score of 16 [40]. One of the widely cited randomized clinical trials using experimental platelet-rich plasma injection to the olfactory cleft showed an effect of 3.67-point (95% CI: 0.05–7.29) in TDI score based on sample size $n=26$ ($n=14$ in treatment arm), the odor ID component is ~ 1.12 points out of 0–16 scale. While these treatment options require invasive and costly (plasma) injection or a prolonged 12-week regimen of training to show the therapeutic effect, our non-invasive smell aids can show similar therapeutic effects immediately after applications and for both general and patient populations.

Another concern is the learning effect, especially given that a 9-item ID may be relatively easy to learn/recognize/memorize. First, the order of testing is being examined as a factor in the linear mixed models and is found to be not significant ($p>0.05$). In addition to that, we further examined the execution of counterbalanced ordering that serves to mitigate the learning effect. In a well-executed counterbalancing design, since each test should occur in one of the four orders (1–4) with equal frequency, the average order of each test should be 2.5. For the odor ID tests among patients, the average orders are baseline = 2.44 ± 1.22, pinch 2.59 ± 1.27, nasal plug up = 2.48 ± 1.02, down 2.46 ± 0.95, all close to 2.5. For the healthy control, first, the threshold testing has less of a learning effect, and second, since threshold measurement can be challenging and time-consuming as stated previously, we have quite a few healthy subjects who did not finish the whole protocol (see missing data)—something we learned and adapted during the course of the study, which is also part of the reason that we switched to odor ID test in later patient testing. So, we adopted an ordering strategy for healthy controls that prioritize baseline and at least one of the manipulations (pinch was selected based on initial data) to be completed by all subjects, and that they are counter-balanced first. The final data showed that baseline occurs first (43%) vs pinch occurs first (57%) are quite well balanced, with slightly more sequences countering the learning effect. Among the healthy controls who finished the nasal plug tests, nasal plug occurs before baseline in only 13% of the sequence, so there could be a learning effect here. But examining the data, nasal plugs actually perform slightly worse than the pinch among the healthy cohort, mitigating some of the concerns. Furthermore, within nasal plug ODTs, the up vs. down directions are well balanced (52% vs 48%).

Other limitations of this pilot study include the lack of long-term comfort and side effects data, and the lack of sample size to perform subgroup analysis of other causes of olfactory losses, beyond COVID-19. Furthermore, it would be interesting to test whether olfactory training could be more effective in conjunction with one of the "olfactory aids"—if more odors are delivered during the training, would that translate to more effective training?—an idea for future study.

## Conclusions

This study demonstrated the potential to enhance olfactory functions in healthy and patient cohorts through improving intranasal air and odorant delivery using two creative yet simple novel smell-aids. The results further broaden our knowledge of the importance of intranasal airflow distribution on olfactory function in both healthy and diseased states, as well as the discovery of novel methods to modulate its distribution. The outcome of this and future continuing research may lead to effective over-the-counter "smell aids" that may have broad applications to professionals who rely on olfaction for their job functions (chefs, perfumers, food/wine critics, fragrant designers, sensory testing experts, etc.), to the general public who want to enjoy better olfactory experiences (food, fragrance, etc.), and to patients with smell loss. Only with a better understanding of the impact of nasal anatomy and its modulation on transport odorants with varying physiochemical properties can we better improve olfactory function through peripheral mechanisms.

#### Abbreviations

| | |
|---|---|
| CFD | Computational fluid dynamics |
| PEA | Phenyl ethyl alcohol (a common rose-like odorant) |
| ODT | Odor detection threshold |
| ID | Identification |
| CI | Confidence interval |

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#### Authors' Contribution

Author contributions: Conceptualization, Methodology, Project administration, Supervision, Funding acquisition: KZ Investigation: VLF, BMS, GZ, KZ Visualization: ZW, KZ Data Analysis: ZW Writing – original draft: KZ Writing – review & editing: KZ, ZW, VLF All authors read and approved the final manuscript.

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#### Data Availability

All data, code, and materials used in the analysis are available to any researcher for purposes of reproducing or extending the analysis via institutional materials transfer agreements (MTAs), contact: zhao.1949@osu.edu.

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by the Ohio State University Institutional Review Board (approval number: 2015H0262), and written informed consent was obtained from all participants.

### Competing interests

A pending US patent has been filed by our institute based on the work presented. As a named inventor in the pending patent, the author (KZ) may participate in the distribution of licensing revenue through the institutional patent policy, however the ownership of the patent and intellectual property is managed by the institute that the author have no input or control. Authors declare that they have no other competing interests.

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