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Humans without a sense of smell breathe differently

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Olfaction may play a restricted role in human behavior, yet paradoxically, its absence in anosmia is associated with diverse deleterious outcomes, culminating in reduced life expectancy. The mammalian nose serves two purposes: olfaction and breathing. Because respiratory patterns are impacted by odors, we hypothesized that nasal respiratory airflow may be altered in anosmia. We apply a wearable device that precisely logs nasal airflow for 24-hour-long sessions in participants with isolated congenital anosmia and controls. We observe significantly altered patterns of respiratory nasal airflow in anosmia in wake and in sleep. These differences allow classification of anosmia at 83% accuracy using the respiratory trace alone. Patterns of respiratory airflow have pronounced impact on health, emotion and cognition. We therefore suggest that a portion of the deleterious outcomes associated with anosmia may be attributed to altered patterns of respiratory nasal airflow rather than a direct result of lost odor perception per se.

There is a common notion that olfaction is an "unimportant" sensory system in humans. This notion was promoted by perhaps the most influential observer of human behavior to date, namely Sigmund Freud[1]. Freud[2], together with the culturally influential Havelock Ellis[3], denigrated the behavioral significance of human olfaction, arguing that olfaction reflected merely "animalistic behavior", and was linked to human behavioral pathology[2]. This 20th-century line of thought remains well-established in 21st-century culture where a poll found that 53% of respondents aged 16–22 would rather give up their sense of smell than give up technology such as cell-phone or laptop[4]. Yet in the face of this notion on an "unimportant sense" stands the painful outcome of lost olfaction, a condition known as anosmia.

The prevalence of anosmia is poorly documented, such that reports range between 1.4% to 15% of the population[5–7] (and 24% above age 53[8]). The reported prevalence for the causes of anosmia also vary widely, but aside of neurodegeneration[9], mostly rank-order as: viral infection (most notably COVID-19[10]), followed by nasal/sinus disease, head trauma, toxins, and congenital anosmias[11] (CA). CA alone likely accounts for ~4% of anosmia cases[12], making for a populational prevalence of about 1 in 10,000[13]. Congenital anosmia can be either syndromic, such as in Kallmann syndrome[14], or isolated (ICA) i.e., of unknown cause. Although there are some known genetic predispositions to ICA[15], and most (but not all[16]) individuals with ICA have significantly reduced or absent olfactory bulbs[17], the functional reason for lost olfaction in ICA remains mostly unknown.

In contrast to the notion of olfaction as an unimportant sense, anosmia is associated with assorted deleterious outcomes, and significantly reduced quality of life[11,18–20]. The negative impact most commonly associated with anosmia, particularly acquired anosmia, is dulled affect and depression[21]. Sufferers often report feelings of personal isolation and emotional blunting[22]. This aspect of life with anosmia garnered significant attention in COVID-19, which is associated with anosmia that may linger far past the viral attack[23]. Sufferers often describe the anhedonia associated with olfactory loss as life-altering[23]. In addition to this primary impact of anosmia, additional consequences include dietary complications[11,18,24], social difficulties[11,18,25], and loss of an important signal for danger, particularly smoke[11,18,26]. This long list culminates in an outcome in acquired

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anosmia where severity is related to 5-year mortality such that (acquired) anosmic older adults have over three times the odds of death compared to normosmic individuals[27].

How does all of the above deleterious cascade occur following the loss of an unimportant sense? One answer is that the notion of olfaction being an unimportant sense for humans is simply completely misguided and wrong[28]. Humans display extensive odor-guided behavior[29], including social behavior[30], and these topics have been reviewed extensively[31,32]. That said, it is still not immediately evident how an acquired-anosmia-derived impairment would relate to a 5-year three-fold mortality rate. With this in mind, a second possible answer is that when loosing olfaction, humans may lose more than odor perception alone. Humans use their nose for two tasks, smelling and breathing, and these two tasks are interconnected, i.e., smelling effects breathing. More specifically, nasal inhalations are shaped by odorant properties in what we refer to as the *sniff-response*, where nasal inhalation magnitude is inversely proportional to odorant intensity and pleasantness[33]. This phenomenon persists even when we are unaware of the odorant in sleep[34] and wake[35], and even in significantly disordered states of consciousness[36]. The impact of odors on respiration is not only event-related as in the sniff-response, it is also ongoing. For example, various concentrations of the odor propionic acid lead to reductions in ongoing inhalation volumes[37], and similarly, different malodors presented during tasks resulted in reduced ongoing inhalation flow[38]. Given the effect of odors on ongoing respiratory patterns, we hypothesized that ongoing respiration may be altered in anosmia. Whereas it is not completely clear how loss of odor perception per se may lead to outcomes such as reduced life expectancy, there are several paths by which altered respiratory patterns may have deleterious physiological outcomes. With this in mind, we set out to compare ongoing nasal airflow in anosmic participants and normosmic controls, with special attention to respiratory patterns that may reflect olfactory exploration. We apply a wearable device that measures nasal airflow for 24-h periods and find significantly altered patterns of nasal airflow in anosmia. Differences include an overwhelming reduction in respiratory peaks (sniffs) during wake, which we attribute to the absence of olfactory exploration in anosmia. Moreover, we observe significant reshaping of the overall anosmic nasal respiratory waveform in wake and sleep. The shift in sleep implies that this alteration goes beyond odor-driven responses alone, and reflects that humans without a sense of smell breathe differently.

Results

Anosmics and normosmics breathe at the same overall rate

We applied a wearable device (Fig. 1A, B) that precisely measures and logs nasal airflow in each nostril separately[39] at 6 Hz (Methods online), in 21 participants with isolated congenital anosmia (ICA) (8 women, 13 men, mean age = 32 ± 7 years) and 31 normosmic controls (19 women, 12 men, mean age = 28 ± 4 years). Participants went about their daily living routine unaltered and returned to the lab 24 hours later to have the device removed and the data downloaded (all the raw data is available online, see "Methods" section). Participants also maintained a daily activity diary, with special attention to registering sleep and wake times. Normal resting respiratory frequency is about 0.25 Hz. Because we measure nasal airflow at about 20 times this rate and use highly sensitive pressure sensors (SDP3x from Sensirion, Stäfa, Switzerland), we can observe local minute within-breath variations in the airflow trace. Thus, we make a clear distinction between respiratory rate and respiratory nasal airflow patterns. This is clarified in Fig. 1, which contains four consecutive breaths from an anosmic participant, which contain 4 respiratory peaks (Fig. 1C), and four consecutive breaths from a normosmic participant, which contain 9 respiratory peaks (Fig. 1D). The added peaks seen in normosmia may reflect exploratory sniffing that can ride on the respiratory wave.

With this distinction between breathing rate and pattern in mind, we first asked whether anosmics breathe at the same overall pace as normosmics. We applied analyses of variance (both Bayesian and parametric) with conditions of Arousal (sleep/wake), and Sense of Smell (normosmic/anosmic) to the automatically identified breaths per minute (BPM) in the respiratory trace (Methods). Bayesian analysis provided strong evidence for an effect of Arousal ($BF_{10} > 150$), no evidence for an effect of Sense of Smell ($BF_{10} = 0.797$), and moderate evidence for an interaction ($BF_{01} = 3.09$, comparing to using arousal only). A parametric analysis of variance similarly uncovered a significant effect for Arousal ($F_{1,50} = 54.8$, $p < 0.001$, $\eta^2 = 0.16$), but no effect for Sense of Smell ($F_{1,50} = 2.5$, $p = 0.12$), nor interaction ($F_{1,50} = 0.49$, $p = 0.49$). This significant effect for Arousal reflected the well-known phenomena of slower respiration during sleep vs. wake (Normosmic sleep: 16.5 ± 2.5 BPM (Median: 17.1 BPM), wake: 18.1 ± 1.6 BPM (Median: 17.9 BPM), $t_{30} = 5.48$, $d' = 0.99$, $p < 0.001$, Bayesian $BF_{10} = 3391$. Anosmic sleep: 15.5 ± 1.9 BPM (Median: 15.5 BPM), wake: 17.4 ± 1.8 BPM (Median: 17.7 BPM), $t_{20} = 4.98$, $d' = 1.1$, $p < 0.001$, Bayesian $BF_{10} = 369$) (Fig. 1E).

Anosmics have significantly less inhalation peaks than normosmics

Having found that normosmics and anosmics breathe at the same overall rate, we next set out to directly test our hypothesis of increased, possibly olfaction-related, exploratory nasal inhalations in normosmia. We observe that the unfiltered unsmoothed respiratory trace often contains several peaks within a single inhalation (Fig. 1D). We therefore applied the same analysis scheme as above to the number of inhalation peaks per minute (IPPM) rather than to the overall respiratory pace. Bayesian analysis provided strong evidence for an effect of Arousal ($BF_{10} > 150$), no evidence for an effect of Sense of Smell ($BF_{10} = 1.459$), yet strong evidence for an interaction ($BF_{01} = 6.641$). A parametric analysis of variance similarly uncovered a significant effect for Arousal ($F_{1,50} = 118$, $p < 0.001$, $\eta^2 = 0.37$), a significant effect for Sense of Smell ($F_{1,50} = 6.3$, $p = 0.016$, $\eta^2 = 0.05$), and a significant interaction ($F_{1,50} = 4.7$, $p = 0.03$, $\eta^2 = 0.015$). This reflected a significantly increased frequency of nasal inhalation peaks in normosmics during wake alone. Specifically, during sleep normosmics nasally inhale at 15.1 ± 3.5 IPPM (Median: 16.3 IPPM) and anosmics nasally inhale at 13.9 ± 3.5 IPPM (Median: 14.4 IPPM) ($t_{50} = 1.2$, $p = 0.23$, Bayesian $BF_{10} = 0.52$), yet during wake normosmics increase nasal inhalation peaks to 23.8 ± 4.5 IPPM (Median: 23.1 IPPM) but anosmics nasally peak at only 19.5 ± 5.8 IPPM (Median: 22 IPPM) ($t_{50} = 3$, $d' = 0.84$, $p = 0.004$, Bayesian $BF_{10} = 6.4$) (Fig. 1F). To further ask whether the difference between anosmics and normosmics during wake was specific to a particular time of day, we ran through the data with a moving average over 1-h blocks. We observed that the difference was consistently significant in all waking hours (Supplementary Fig. 2). This added four IPPM in controls amounts to a remarkable added ~240 inhalation peaks per hour in normosmia over anosmia. In other words, consistent with our hypothesis, ongoing daily patterns of respiratory nasal airflow are profoundly altered in anosmia. This difference is pervasive, and its depiction in Fig. 1 was consistent across the entire cohort (Supplementary Fig. 1).

One may ask whether the increased IPPM in normosmia reflected a response to a fluctuating olfactory environment in this naturalistic experiment or, in turn, whether it reflected a fixed shift in normosmic vs. ansomic nasal inhalation patterns, regardless of odors. To address this, we tested an additional cohort of 32 normosmic participants in an odorant-free room. This is an experimental room coated in odorant non-adherent materials, and subserved by high throughput HEPA and carbon filtration. We observe that under these odorant-free conditions, the rate of IPPM in normosmia was 17.2 ± 3.3 (Median: 17.6 IPPM), a value not significantly different from that previously observed in

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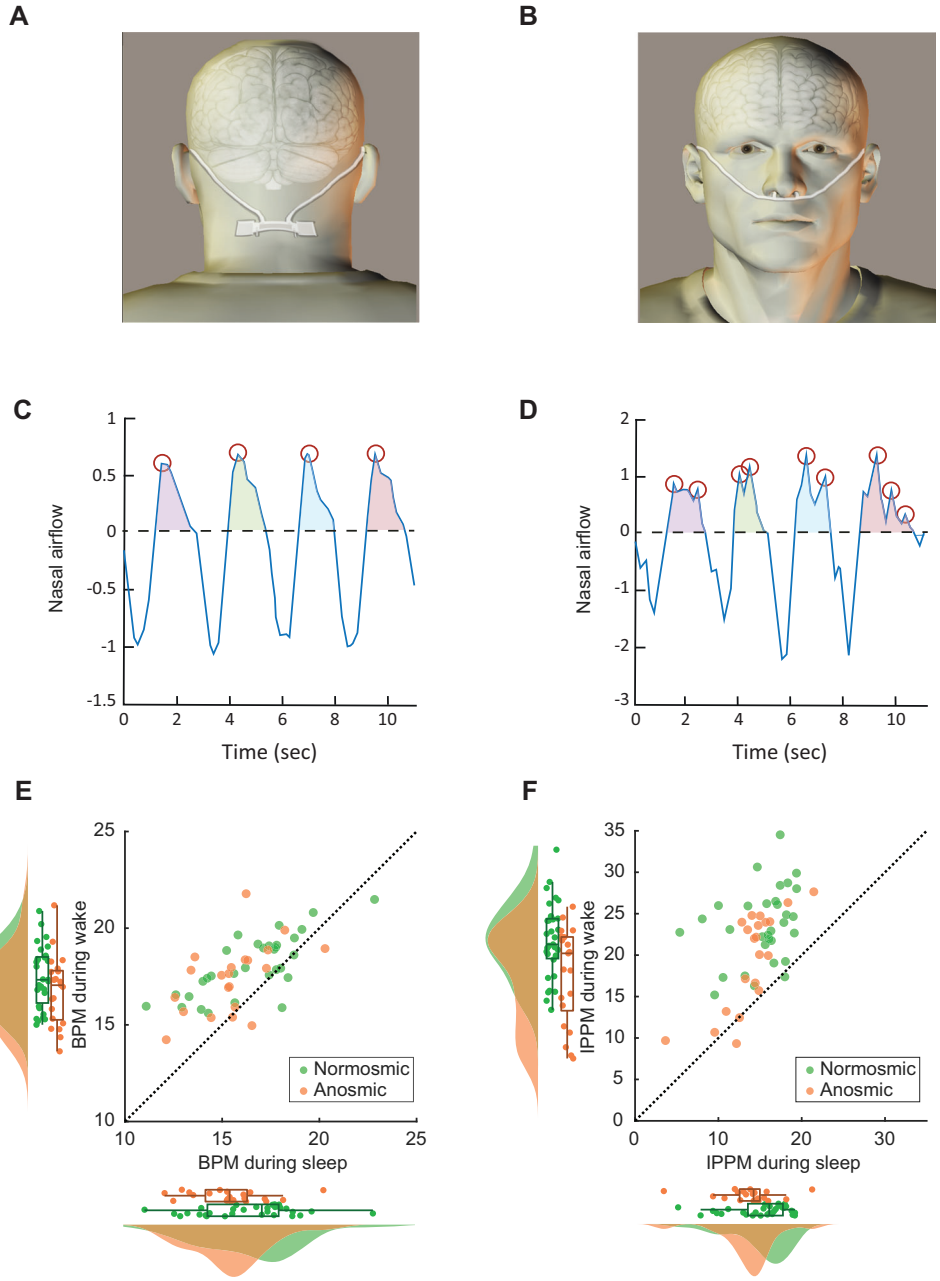

Fig. 1 | Distinguishing between respiratory rate and respiratory peaks. **A**, **B** An illustration of the wearable device, attached to **A** the nape of the neck and **B** connected by nasal cannula to measure nasal airflow in each nostril separately. **C** Four consecutive breaths from an anosmic participant. Peaks identified by the software circled in red. Here total breath count is 4 and number of inhalation peaks is also 4. **D** Four consecutive breaths from a normosmic participant. Peaks identified by the software circled in red. Here total breath count is also 4 yet the number of inhalation peaks is 9. Samples from all participants, 21 anosmics and 31 normosmics, are depicted in Supplementary Fig. 1. **E** Breaths per minute (BPM) during sleep and wake in normosmia (green) and anosmia (orange), plotted along the unit-slope line (dotted line $x = y$), with raincloud plots and probability density. An rmANOVA uncovered a significant effect for Arousal ($F_{1,50} = 54.8$, $p < 0.001$, $\eta^2 = 0.16$; Normosmics sleep vs. wake: $t_{30} = 5.48$, $d' = 0.99$, $p < 0.001$. Anosmics sleep vs. wake: $t_{20} = 4.98$, $d' = 1.1$, $p < 0.001$), but no effect for Sense of Smell ($F_{1,50} = 2.5$, $p = 0.12$), nor interaction ($F_{1,50} = 0.49$, $p = 0.49$). **F** Inhalation peaks per minute (IPPM) during sleep and wake in normosmia (green) and anosmia (orange), plotted along the unit-slope line (dotted line $x = y$), with raincloud plots and probability density. An rmANOVA uncovered a significant effect for Arousal ($F_{1,50} = 118$, $p < 0.001$, $\eta^2 = 0.37$), a significant effect for Sense of Smell ($F_{1,50} = 6.3$, $p = 0.016$, $\eta^2 = 0.05$), and a significant interaction ($F_{1,50} = 4.7$, $p = 0.03$, $\eta^2 = 0.015$). Post hoc analysis revealed significantly increased frequency of nasal inhalation peaks in normosmics during wake ($t_{50} = 3$, $p = 0.004$, $d' = 0.84$) but not during sleep (Normosmics vs. anosmics: $t_{50} = 1.2$, $p = 0.23$). For panels **C** and **D**, the area for each separated inhale colored with different arbitrary color, and the nasal airflow is given in arbitrary units. For panels **E** and **F**, each circle is the mean of a participant, bars are the group mean, lines are the standard error of the mean and group size is anosmia $n = 21$, normosmia $n = 31$. The boxplots in these panels represent data distribution, with the box extending from the first to the third quartile and a solid line indicating the median. The whiskers extend to the furthest data points that are within 1.5 times the interquartile range.

anosmia ($t_{51} = -1.91$, $p = 0.06$). We acknowledge that the information in this control is limited by the fact that, unlike the naturalistic main experiment where participants were also moving out and about, here they were seated in a room, and this difference between moving about vs seated will obviously reflect in respiratory patterns, regardless of smells. With this limitation in mind, this control nevertheless implies that the added IPPM in normosmia likely reflects interaction with an odor environment.

The anosmic breathing waveform significantly differs from the normosmic waveform

To this point, we first analyzed the overall respiratory rate, where we saw no difference in anosmics. We next analyzed the rate of inhalation peaks, which we associate with olfactory exploration. Here we saw a significant decrease in anosmics, which behaved throughout the active day like normosmics seated in an odorless room. To now further gauge whether nasal respiratory flow is altered in anosmia beyond IPPM alone we took advantage of a recently developed toolbox for parametrization of nasal airflow, which defined 24 time-domain parameters[40]. To this set of parameters, we now also add the above-defined IPPM, and derive each parameter for sleep and wake separately, culminating in 50 parameters (25 for wake and 25 for sleep). We then culled 23 parameters with particularly high intercorrelation ($|r| > 0.7, p < 1 \times 10^{-7}$) as they will lack added information, resulting in a list of 27 informative parameters (Supplementary Table 1). We then compared anosmics and normosmics on each of these measures (Fig. 2A). We observed significant differences in 8 of these parameters, with four parameters surviving additional cutoff following Benjamini–Hochberg correction for multiple comparisons (corrected $p < 0.0074$). At this cutoff, we observe significant differences in "Percent of breaths with inhale pause in wake" (mean anosmic: 81% ± 7%, mean normosmic: 75% ± 7%, $t_{50} = 3$, $p = 0.004$, $d' = 0.85$) (Fig. 2B), "IPPM in wake" (mean anosmic: 19.5 ± 5.8, mean normosmic: 23.8 ± 4.5, $t_{50} = -3$, $p = 0.004$, $d' = -0.84$) (Fig. 1F), "CoV of inhale volume in sleep" (mean anosmic: 0.34 ± 0.08, mean normosmic: 0.29 ± 0.04, $t_{50} = 2.98$, $p = 0.004$, $d' = 0.84$) (Fig. 2C), and "Exhale peak value in wake" (mean anosmic: 1.57 ± 0.37, mean normosmic: 1.81 ± 0.24, $t_{50} = -2.82$, $p = 0.007$, $d' = -0.8$) (Fig. 2D). Put in words, in addition to the previously noted reduction in IPPM, ansomic respiration is characterized by added inhalation pauses and reduced exhalation peak flow in wake, and increased covariance of inhale volume in sleep.

We can classify anosmia from breathing alone without the use of odors

Given these differences that all had meaningful effect sizes (all $|d'| > 0.8$), we set out to ask if we could classify anosmia without odors, based on respiratory patterns alone. We entered the 4 parameters that survived correction into a KNN classifier and tested using a leave-one-out scheme such that testing was performed on participants, not in the learning set. We obtained a receiver operating curve (ROC) with the area under curve of 79% (Fig. 2E), providing for 83% classification accuracy, with 67% true positive rate (anosmics classified as anosmics) and 94% true negative rate (normosmics classified as normosmics). To estimate the significance of this classification, we repeated the process 10,000 times, each time randomly shuffling the "anosmic" and "normosmic" labels. This provided for a chance distribution of classification accuracies. We observed no better classification in any of these iterations, such that the significance of our classification is $p = 0.0001$ (Fig. 2F). In other words, we can determine congenital anosmia at 83% accuracy without using any odorant in our test. We note that this result was not dependent on the previously identified measure of IPPM, as rerunning the classifier without IPPM still achieved 81% accuracy, $p = 0.0001$ (Supplementary Fig. 3), yet the classifier was highly dependent on "CoV of inhale volume in sleep", and rerunning the classifier without this parameter reduced classification to 62%, $p = 0.06$ (Supplementary Fig. 3). The fact that anosmic respiration differed from normosmic respiration in sleep in five respiratory parameters at $p < 0.05$ (and in one following correction), implies that anosmic respiration is also altered regardless of odorant sampling. We state this as olfactory sleep responses were evident only when high-concentration odorants were pumped by olfactometer to the nose of sleeping participants[34], yet here the natural sleeping olfactory environment remains largely constant. Thus, the differences we observe between anosmics and normosimics in sleep are unlikely to reflect responses to odors. Finally, by measuring airflow in each nostril independently, we could also address the possibility of an altered nasal cycle[39] in anosmia, yet we found no evidence for this (Supplementary Fig. 4).

Discussion

Because odors influence respiration[37,38], we hypothesized altered nasal airflow in anosmia. We observed two types of differences: During the wake, normosmia was associated with a pronounced increase in the rate of respiratory peaks. This effect disappeared when normosmics were seated in an odorless room. Despite the unavoidable limitations of the odorless room control, it implies that the increased peaks in normosmia may reflect odor-driven exploration. In turn, we observed additional differences in nasal airflow parameters, many of them persistent or, in fact, increased during sleep. We therefore speculate that through life development without olfaction, the respiratory pattern is shifted in congenital anosmia. Such shifted respiratory patterns, and particularly nasal airflow patterns, may have an impact on physiological and mental health.

A dramatic example of the possible impact of respiratory airflow patterns on health is the importance of *sighing*, which was uncovered following the advent of steel lungs to treat polio. Despite full-volume artificial respiration, many early patients receiving artificial ventilation were dying. It quickly became apparent that to maintain life, patients need not only to breathe rhythmically, but also sigh every 5 min or so, as this is critical for preventing collapse of alveoli in the lungs[41]. In other words, beyond respiratory rate alone, the intricate dynamic patterns of respiratory airflow can be highly consequential for health.

Beyond the general physiological state, respiratory patterns have significant implications particularly on neural state[42,43]. Nasal airflow orchestrates volleys of neural activity throughout the brain, such that every sniff is associated with a cascade of activity spreading from the olfactory bulb and throughout the cortex[44]. The current study implies that normosmics experience an added ~240 such neural waves per active waking hour over anosmics. This is potentially a profound difference in brain activity. Consistent with this, resting-state brain activity is indeed altered in acquired anosmia[45,46], yet inconsistent with our hypothesis; functional connectivity was not altered in congenital anosmia[47]. Consequent to nasal-airflow-induced patterns of brain activity, patterns of airflow have been linked to emotional[48] and cognitive[49–53] states. More specifically, patterns and particularly phase (inhale vs. exhale) of nasal airflow have been linked to performance in memory consolidation[49] and retrieval[50], quality of mental imagery[51,52], discrimination of facial fear[50], and visuospatial processing[53]. Given all of these implications, although we acknowledge the many other well-recognized potential explanations for the untoward morbidities and mortality of individuals with olfactory loss, we submit that it is now plausible that a portion of the deleterious outcomes associated with anosmia may be related to altered respiratory patterns.

This study and our method have several limitations we would like to acknowledge. First, we would have preferred to sample at a higher frequency, e.g., 25 Hz, which is recommended for extracting respiratory nuances[54]. Our lower sampling rate reflected a power-consumption constraint, as had we sampled any faster, we could not have maintained a 24-h recording. Thus, there may be additional differences we failed to capture. Second, our method is oblivious to oral airflow. Although we think our particular interest in nasal airflow is justified, it is very possible that measures of oral airflow may have added to this picture. Third, an oversight of our study was not to formally verify normal olfaction in the control participants. Although they all self-reported an intact sense of smell, this does not assure healthy olfaction[20,55]. However, we note in this respect that if there were participants with impaired olfaction in the control group, this could only reduce the reported effects, not drive them. Finally, it will

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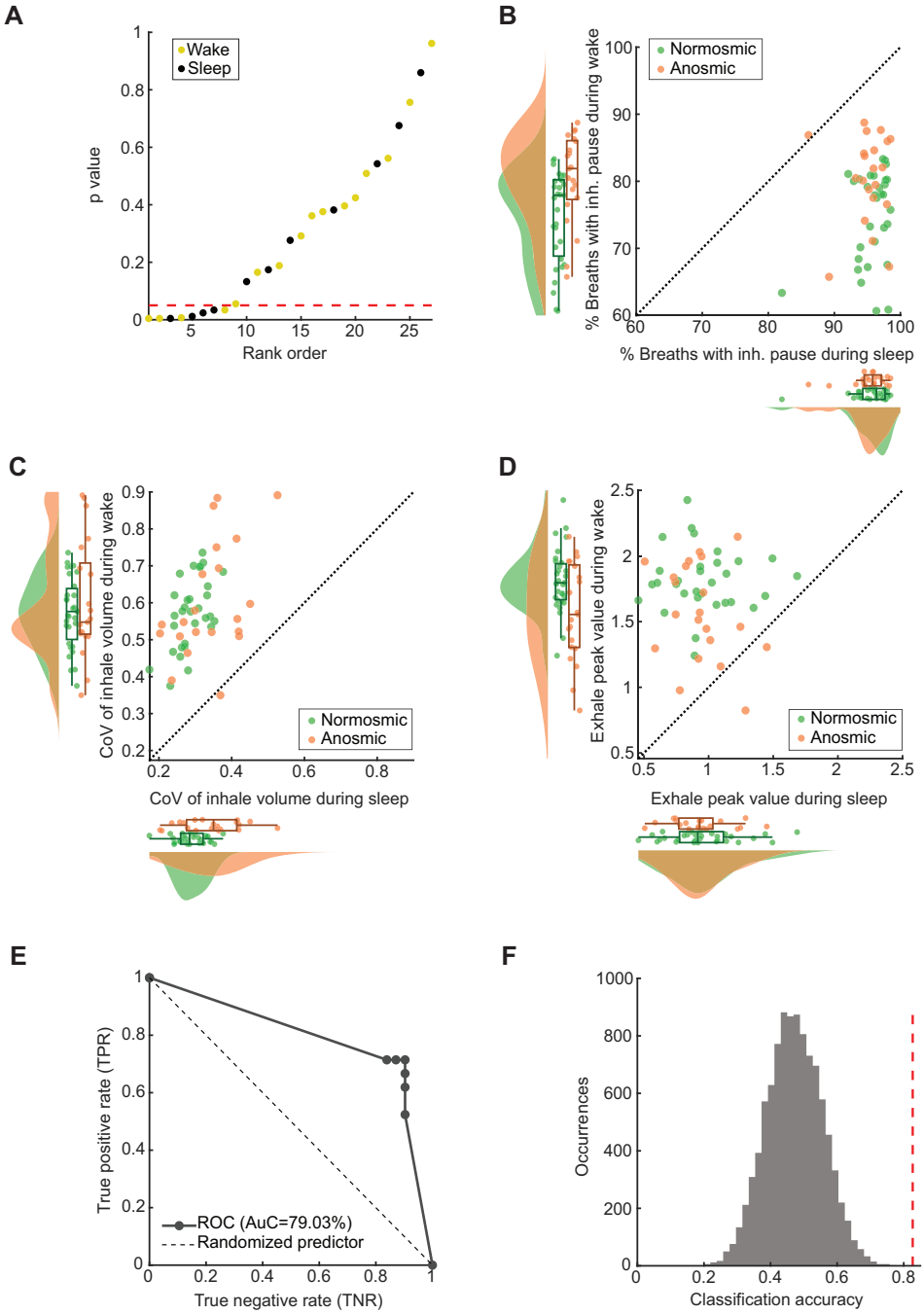

Fig. 2 | Classifying anosmia without using odorants. A A comparison of anosmics vs. normosmics along 27 nasal respiratory parameters, rank-ordered by the extent of difference across groups (using two-sided *t*-test), with a horizontal line for (uncorrected) $p = 0.05$, where yellow dots represent parameters in wake and dark grey dots represent parameters in sleep. Following Benjamini-Hochberg correction for multiple comparisons (corrected $p < 0.0074$), we found four parameters below the corrected threshold. **B** Percent of breaths with inhale pause during sleep and wake in normosmia (green) and anosmia (orange). A two-sided t-test between the groups in wake revealed a significant difference ($t_{50} = 3$, $p = 0.004$, $d' = 0.85$). **C** Coefficient of Variation (CoV) of inhale volume during sleep and wake in normosmia (green) and anosmia (orange). A two-sided *t*-test between the groups in sleep revealed a significant difference ($t_{50} = 2.98$, $p = 0.004$, $d' = 0.84$). **D** Mean exhale peak value during sleep and wake in normosmia (green) and anosmia (orange). A two-sided *t*-test between the groups in wake revealed a significant difference ($t_{50} = -2.82$, $p = 0.007$, $d' = -0.8$). **E** The receiver operating characteristic curve from the KNN classifier applied to the airflow data. **F** The distribution of 10,000 classifications on shuffled data, with the actual classification accuracy marked by the dotted red line. For all panels, group size is anosmia $n = 21$, normosmia $n = 31$. For panels **B**–**D**, the measurements are plotted along the unit-slope line (dotted line $x = y$), with raincloud plots and probability density, where each circle is the mean of a participant, bars are the group mean, and lines are standard error of the mean. The boxplots in these panels represent data distribution, with the box extending from the first to the third quartile and a solid line indicating the median. The whiskers extend to the furthest data points that are within 1.5 times the interquartile range.

be interesting to add a future comparison to acquired anosmia as well. Are these respiratory changes immediate after olfactory loss? Do they develop over time? Or do they develop at all in acquired anosmia? We have no answers to these questions in the current study.

Despite these limitations, we think we provide convincing evidence for the main claim of this study, namely that people with congenital anosmia breathe differently. One may ask how was this difference not observed previously. We note that long-term

respiration is typically measured with piezoelectric respiratory belts or derived from plethysmography (RRp), and these almost always contain an inherent 3 Hz low-pass filter. Critically, we further observe that if we apply a 3 Hz low-pass filter to our data, the difference between anosmics and normosmics completely disappears (shift from $t_{50} = 3$, $d' = 0.84$, $p = 0.004$, Bayesian $BF_{10} = 6.4$ to $t_{50} = 0.2$, $d' = 0.08$, $p = 0.85$, Bayesian $BF_{10} = 0.37$). In other words, long-term measurement of respiratory airflow without low-pass temporal filtration can uncover meaningful information. In this study, it uncovered altered breathing patterns in anosmia.

Methods

Participants

All participants provided written informed consent to procedures approved by the Weizmann Institute IRB committee. To estimate the necessary sample size, we applied a power analysis[56] assuming a large effect size ($\eta^2 = 0.14$)[57]. We find that at an alpha level of 0.05 and 90% power we need to study at least 20 participants per group. With this in mind, we recruited 21 anosmics (8 women, 13 men, mean age = 32 ± 7 years) and 31 normosmics (19 women, 12 men, mean age = 28 ± 4 years). Gender was self-reported. With the limited availability of participants with congenital anosmia in mind, we made an effort to equate the number of men and women, and we did not enter gender as a factor in the analysis, as the group size would be too small. All participants with anosmia underwent nasal endoscopy and medical history review by an ENT physician (co-author SS) to rule out non-congenital causes of anosmia. All anosmics reported a lifelong absence of olfactory perception without any memory of odors and scored as "Anosmic" on the University of Pennsylvania Smell Identification Test (UPSIT)[58] (mean score = 11.1 ± 3, highest score = 17). Anatomical MRI scans revealed no or neglected olfactory bulbs in all anosmics. Normosmic participants were all in general good health, with no reported history of neurological or mental illness, and had neither olfactory deficits nor chronic or acute conditions that involved the respiratory tracts. All participants were asked to rate their own sense of smell on a scale from 1 (poor) to 9 (excellent). Anosmic self-ratings were mean = 1.1 ± 0.4, yet normosmic self-ratings were 7.5 ± 1.2. The lowest self-rating in normosmia was 5. All participants were compensated for their participation at a rate of 400 NIS (equivalent to ~100 USD).

Data acquisition

Nasal airflow was acquired using a device we previously described in detail[39]. For the final 11 participants, we used a further miniaturized version of the same device that we call the Nasal Holter, as seen in Fig. 1. In brief, the device is a wearable logger that uses a "stereo" nasal cannula to measure pressure in each nostril separately and converts the pressure time-series into a flow time-series. The data is acquired at 6 Hz (part of the data was acquired at 5.5 Hz, specified in Supplementary Data File 1), and stored within the device for-later download. Additionally, all participants maintained a daily diary of activity, with special emphasis on logging sleep and wake times.

Parameterization

All data were analyzed using MATLAB R2020a (MathWorks) and customized code. In order to derive respiratory parameters, we split the nasal airflow trace into 5-min blocks and used the activity diary to label each block as "Sleep" or "Wake". We then used a standard respiratory signal processing toolbox, BreathMetrics[40], to extract respiratory features. Additionally, we applied a standard peak-finding algorithm to extract the number of inhalation peaks per minute (https://www.mathworks.com/help/signal/ref/findpeaks.html). Subsequently, we calculated the average of each parameter from all 5-min blocks with the same label (Sleep/Wake).

Statistical analysis

All statistical analysis was done using JASP (version 0.14.1)[59]. All airflow properties were analyzed using a repeated-measures analysis of variance (rmANOVA), with a sense of smell (normosmic/anosmic) as a between-subjects parameter and arousal (Sleep/Wake) as a within-subject parameter. For statistical comparison between normosmic and anosmic individuals, independent-sample *t*-tests were used. For statistical analysis within each group, matched-sample t-tests were used. The power of the effects was estimated by calculating Cohen's *D* (*d'*). The significance of the classifier was assessed using bootstrapping with 10,000 iterations. Additional estimation of the strengths of the effects was assessed by Bayes factors BF_{10} when comparing to the null model and BF_{01} when comparing to the best model[60] with uniform priors.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All the raw data for this manuscript is available at https://gitlab.com/liorg/anosmics-breathe-differently/-/tree/main/Data. Source data are provided with this paper.

Code availability

The custom code used to process the data collected in this study is available at https://gitlab.com/liorg/anosmics-breathe-differently.

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Author contributions

Developed the concepts: L.G. and N.S. Built device hardware: A.W. Wrote device software: D.H. Examined anosmic participants: S.S. Designed experiments: L.G., R.W., and N.S. Ran experiments: L.G. and R.W. Analyzed data: L.G., T.S., and N.S. Wrote first draft of paper: L.G. Edited final draft of paper: L.G., A.W., D.H., R.W., T.S., S.S., and N.S.

Competing interests

All authors (L.G., D.H., A.W., R.W., T.S., S.S., and N.S.) have co-authored a patent application by The Weizmann Institute of Science for classifying anosmia by nasal airflow. Authors D.H., A.W., and N.S. have applied for a patent on the device used to measure nasal airflow, and have financial interests in a startup company developing this device (although not for anosmia). The startup company had no link to the current study.

Additional information

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