Respiration-Triggered Olfactory Stimulation Reduces Obstructive Sleep Apnea Symptoms Severity – A Prospective Pilot Study

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ABSTRACT

Study Objectives: Obstructive sleep apnea (OSA) is a prevalent sleep-disordered breathing condition characterized by repetitive cessations in breathing during sleep. Current standard of care for OSA management is continuous positive air pressure (CPAP) devices, which often suffer from low tolerance due to limited adherence. Capitalizing on the unique neurocircuitry of the olfactory system and its retained function during sleep, we set out to test the feasibility of transient, respiration-based olfactory stimulation as a treatment for OSA symptoms.

Methods: Thirty-two OSA patients (AHI $\geq$ 15 events/hour) were recruited and underwent two polysomnography sessions, 'Odor' and 'Control', counterbalanced for order. In 'Odor' night, patients were presented with transient olfactory stimulation delivered via a computer-controlled olfactometer. The olfactometer, equipped with a wireless monitoring unit, analyzed respiratory patterns and presented stimulation upon detection of respiratory events. No odor was presented 'Control' nights.

Results: Olfactory stimulation reduced AHI (Apnea-Hypopnea Index) (n = 17, 49.2±10.2 years, range: 30–66; $p = 0.02$, $BF_{10} = 115.85$), reflecting an average decrease of 31.3% in the number of events. Post hoc planned comparisons revealed a reduction in HI (Hypopnea Index) ($p = 0.02$, $BF_{10} = 2.39$), but not AI (Apnea Index) ($p = 0.26$, $BF_{10} = 1.56$). This effect was not linked to baseline symptoms severity ($\rho = -0.042$, $p = 0.87$) and did not vary across odorants ($F(4,64) = 0.56$, $p = 0.67$). Finally, olfactory stimulation did not affect sleep structure (all $p > 0.44$, all BF01 > 2.9).

Conclusions: Olfactory stimulation during sleep was effective in reducing OSA symptoms severity and may provide a novel treatment modality, therefore prompting continued research on this front.

INTRODUCTION

Sleep apnea, a sleep-disordered breathing condition, is characterized by repetitive cessations in breathing while asleep, lasting 10 seconds or more. The majority of sleep apnea cases is due to collapse of the soft tissue of the upper airways and is thus termed "obstructive sleep apnea" (OSA). The acute hypoxia caused by recurrent cessations of breathing produces multiple, brief, arousals sufficient to restore muscle tone and activate voluntary breathing [1]. The impact of frequent breathing cessations and sleep fragmentation on health and quality of life is devastating. Sleep apnea is linked with deleterious effects on daytime cognitive function such as impairment of attention [2], memory [3] and even onset of depression [4]. Apart from cognitive impairment [5], sleep apnea is associated with increased morbidity and mortality as a result of both short (traffic- and work-related accidents) [6] and long-term consequences resulting from cardiovascular conditions, arrhythmia, and stroke [7,8]. OSA is an alarmingly prevalent disorder, with conservative estimations suggesting at least 7-9% of the general adult population are afflicted with OSA to some degree [9,10].

Since its introduction over four decades ago, continuous positive airway pressure (CPAP) treatment has served as the primary treatment modality for OSA. While CPAP is a highly effective treatment for OSA, adherence to its treatment regime is often sub-optimal; To reach clinical efficiency, minimally acceptable levels of adherence to CPAP are at least four hours of treatment during sleep per day [11] yet estimates suggest only 30%–50% of patients reach this criterion while others are often compelled to seek other treatment avenues or go untreated [12]. In addition, chronic CPAP use is associated with substantial short-term and long-term side effects such as nocturnal awakenings, oral dryness and naso-oral soreness [13,14]

There are some alternatives to CPAP treatment with varying level of success. These range from naso-oral appliances (e.g., mandibular advancement devices [15,16]), to more invasive procedures such as electrical stimulation of the hypoglossal nerve and pulse generator-induced stimulation of the upper airway muscles [17]. Most of these alternatives are less affective or carry various risks (invasive procedures) or financial burden and thereby positive air pressure masks remain the standard of care for efficient reduction of OSA symptoms. This situation calls for the development of more tolerable solutions for OSA management.

In the search for an effective minimally-encumbering, noninvasive treatment for OSA, a central sensory pathway has been largely overlooked – olfactory stimulation during sleep. Previous studies established that olfactory stimulation possesses a unique combination of traits that are particularly attractive for OSA treatment: First, it is largely held that purely olfactory and mildly trigeminal odorants (trigeminality is defined as the ability to stimulate the branch of the trigeminal nerve nested within the olfactory epithelium [18]) do not wake from sleep [19–23]. Furthermore, there is multiple evidence to support sleep-benefiting effects of olfactory stimulation [24] during sleep, in health [25,26] and in clinical settings [27,28]. Second, and critically, despite not inducing arousal, the incoming olfactory sensory information is picked up by the sleeping brain to influence physiology [19], cognition [23,29–31], and most importantly in the case of sleep-related breathing disorders – respiration.

One core feature of olfactory processing is the 'sniff response', a sensorimotor loop by which presentation of odorants induces change in nasal airflow often according to intensity or valence. This direct link between sensory input and respiratory mode, which was studied thoroughly in wake humans [32,33], is maintained during sleep [22,34,35]. Specifically, olfactory stimulation during sleep modulates sniff parameters such as volume and duration in several subsequent respiratory cycles during both NREM and REM sleep. Thus, given that odors manipulated respiration during sleep without leading to arousal, it is conceivable to improve symptoms in breathing disorders in

sleep by actively introducing olfactory stimulation to counteract events of respiratory cessation. A few studies have attempted to harness the link between olfaction and respiration in clinical settings where respiratory disorders are of concern, such as on apnea of prematurity in preterm neonates [36–38] but not as a treatment for adult OSA. In addition, in most of these studies the methods of odor delivery in sleep relied on in-room essential oil diffusers or a single acute exposure before sleep. Therefore the benefits of such stimulation methods likely to decay over time due to sensory habituation [39]. A first effort to modulate respiratory patterns in healthy adults participants using odors was attempted by Arzi and Sela [22] who reported that transient olfactory stimuli during sleep modulated the inhalation/exhalation ratio in several subsequent respiratory cycles.

With this in mind we set out to test the feasibility of transient, respiration-based olfactory stimulation as a treatment for OSA symptoms. Specifically, in this study we presented olfactory stimulation to OSA patients using a computer-control olfactometry device. Importantly, concurrent with the contemporary framework of personalized medicine, in which treatments are customized to optimally fit individual needs, the olfactometer monitored patients' respiratory patterns and presented the odors in a targeted manner upon detection of apnea events.

METHODS

Patients

Thirty-two (7 women, 25 men, age 50.4 ± 9.7 years) patients with a preexisting diagnosis of OSA with a severity threshold defined by Apnea-Hypopnea Index (AHI) $\geq$ 15 events/hour polysomnography (PSG) were recruited and provided informed consent to participate in the study. Apnea severity and its clinical classification may change over time and in different sleeping conditions [40–42]. The time gap between OSA diagnosis and participation in the

experiment was 476 ± 507 days in this cohort. Thus, in order to evaluate participants' OSA severity in the experimental setting at baseline we used the PSG measures recorded during the night without olfactory stimulation ('Control', 'C'). Inclusion criteria were, age 30-70 years, mild to severe OSA with an apnea-hypopnea index (AHI) ≥15 events/hour on baseline night ('Control', 'C') at the sleep lab, body mass index (BMI) < 35, and normal sense of smell. Exclusions criteria were the use of antipsychotic or hypnotic drugs, drug abuse, chronic lung disease, congestive heart failure, primary neurological diagnosis, any known allergy to odorants used during the study, history of severe nasal allergies or sinusitis or difficulty breathing through the nose, any previous operation or trauma to the nose from the last five years, previous diagnosis of insomnia, narcolepsy, periodic limb movement disorder, respiratory failure, major neurological diagnosis, epilepsy, CPAP dependency according to investigator discretion, and COVID-19 diagnosed in recent 3 months.

Exclusion criteria occurrence in the recruited cohort are listed in Table 1. The demographics and clinical data of patients included in the study are detailed in Table 2. Following exclusions, the study cohort comprised of 17 patients (4 women, 13 men, age 49.2 ± 10.2 years, range: 30 – 66) patients.

Study Design

This prospective, within-subject study was conducted at Assuta Medical Center, Tel-Aviv, and Shaare Zedek Medical Center, Jerusalem, Israel, between October 2020 and September 2021. The study was registered in the online database clinicaltrials.gov (NCT04609618) and was approved by both medical centers' ethics committees (E.C. #0045-20, E.C. #0560-20).

The study design comprised of two nights: treatment ('Odor') in which olfactory stimulation was delivered, and control ('Control'), in which participants slept in the same PSG setting but with no

odor delivery, or any other OSA-related aid. The two conditions were counterbalanced for order. The treatment and control night took place 7.6 ± 4 (M ± SD) days apart (Note that time between sessions was calculated with the exclusion of one patient who had to be summoned for a third session which took place 177 days following their previous visit, due to a technical issue with data recording in one of the nights).

OSA Severity Classification

The number of apneas and hypopneas per hour of sleep is collectively termed the apnea–hypopnea index (AHI). A hypopnea was defined as a reduction usually > 30**%** in airflow and/or effort, lasting > 10 seconds and accompanied by an arousal or a fall in SaO2 of > 3%.

An AHI of 5 or more events per hour is a cutoff for of OSA diagnosis. The AHI is further used to categorize OSA severity; patients with AHI of 5 to 15, 16 to 30, or more than 30 events per hour, are considered to have mild, moderate, or severe OSA, respectively [43]. In the 'Control' nights OSA severity, measured by the Apnea-Hypopnea index was 31.65 ± 16.88, range: 15.2 - 83.5. According to these baseline measurements, nine (53%) participants were labeled with moderate OSA and eight (47%) participants with severe OSA. An additional measure used in OSA symptomatology is the Oxygen Desaturation Index (ODI) defined as a 3% or more decrease in blood oxygen saturation (SpO_2) below baseline.

Polysomnography and sleep quality

Polysomnography (PSG) was conducted and scored using the SOMNOscreen PSG platform (SOMNOmedics, Germany). The same recurring staff of sleep lab technicians in each center performed sleep data processing in accordance with the American Academy of Sleep Medicine

(AASM) [44]. PSG staff members were blind to the experimental conditions which were randomly assigned for each night. PSG montage consisted of a 6-lead electroencephalogram (EEG), two bilateral electrooculograms (EOG) leads, one submental lead, two tibial electromyograms (EMG), and one electrocardiogram (ECG) lead. Respiratory measurements in the PSG setup were evaluated from chest wall and abdominal movement using plethysmography as well as nasal pressure sensors and thermal airflow signals. Oxygen saturation and heart rate were monitored using a pulse oximeter. In addition, end-tidal carbon dioxide signals were obtained ($EtCO_2$) (Respironics, USA). Lastly, sleep position, and audiovisual recordings were collected.

Processed data exported from the PSG platform included sleep continuity parameters, latency to stage 1 (SL1) and stage 2 (SL2), percent of time in wake after sleep onset (%WASO), index of awakenings, total sleep time (TST), and percent of time in bed (%TIB). Sleep architecture parameters consisted of percent of time spent in stage N1 stage N2 rapid eye movements (REM) (%REM), and slow-wave sleep (SWS) (%SWS), index of sleep stage changes, and REM onset latency (ROL).

Sleep quality questionnaires obtained during screening confirmed that the cohort, on average, reported poor sleep quality. The average Pittsburgh Sleep Quality Index (PSQI) score was 5.42 ± 3.47, with a score of five typically serving as criterion for effectively distinguishing good and poor sleepers [45] ; Similarly, average Epworth Sleepiness Scale (ESS) score was 9.88 ± 5.85 which is indicative of higher-normal daytime sleepiness [46].

Olfactory stimulation

Odorants: All patients were presented with a fixed repertoire of five odor mixtures based on essential oils: orange, eucalyptus, lavender, frankincense-cinnamon and geranium (Phyto-Active, Israel). All odor materials held certificate of conformity with International Fragrance Association

(IFRA) standards. Across the cohort, there was only a single case of a mild adverse event, feeling of nausea, that has been adjudicated as possibly related to the olfactory stimulation. No serious adverse events have been reported.

Olfactometer: Olfactory stimulation was carried out using a computerized olfactometer which is a commercial product designed to present odors at predefined times, for example in this study when an apnea event is detected (Scentific™, Appscent Medical). The olfactometer consisted of the following main components: a respiration detector, a controller, an odor disperser, and an odor cartridge (Fig. 1a). The respiration detector was equipped with a diagnostic system capable of online monitoring of patients' respiratory patterns based on Impulse Radio Ultra-Wideband (IRUWB) radar [47–49]. The controller unit detected movement patterns associated with the onset of apnea-hypopnea epochs which then triggered odor delivery. Finally, the odor disperser consisted of a computer-controlled, and a low-pressure compressed air compartment in which disposable odorant cartridges were housed.

We positioned the odor disperser at about 50 cm from the patient's head to target odor delivery at the vicinity of the nose. This setup allowed an odorous environment at the nose, devoid of other visual, tactile, humidity, or thermal stimuli.

Personalized odor delivery regimen: The olfactometer constantly monitored respiratory patterns. When an apnea was automatically detected one of the five odors was presented approximately one second later for a period of 20 seconds, concluding with an inter-stimulus-interval of 40 seconds. Detected apnea events did not trigger odor presentation if they occurred within the ISI. The olfactometer rotated between five odors, presenting them in a random order to prevent olfactory habituation. Following each odor burst, non-odorous room air was emitted from the nozzles for three seconds to reduce odor contamination to the tubing (Fig. 1b). Apnea detection was based on a decision-tree algorithm, initially trained on 392 IRUWB signal features which were subsequently optimized to 20-feature repertoire. Critically, the olfactometer did not

counteract apnea-hypopnea events only once they met the minimal duration of 10 seconds as clinically defined, but attempted to constantly predict their occurrence ahead of time. We first assessed the olfactometer's apnea-hypopnea detection rate by comparing apnea-hypopnea events onsets between the olfactometer and the PSG, which underwent manual inspection by experienced sleep technicians. Since the olfactometer logged apnea-hypopnea events both in the 'Odor' condition and 'Control' (without applying the odor stimulation), we inspected both data sets. The olfactometer's detection rate for events marked by the PSG was 46.01 ± 22.03 %. Detection rates did not differ between 'Odor' and 'Control' nights ('Odor': 46.24 ± 21.10 %, 'Control': 45.78 ± 22.93 %, non-parametric test: $z = -0.10$, $p = 0.92$, $BF_{10} = 0.25$).

Overall the olfactometer presented 115.52 ± 66.21 (Table 3) odor pulses per treatment night. We carried out a complementary analysis, in which we calculated the olfactometer's apnea-hypopnea events assessment rate and decision to deliver an odor in the presence and absence of PSG-verified apnea-hypopnea events (termed 'conjunction' and 'non-conjunction', respectively). The decision to deliver an odor occurred at 25.46% ± 18.99 of the cases when an apnea-hypopnea event was detected by the PSG and 74.54% ± 18.99 when not related to an event detected by PSG (see discussion and Table 3).

Data analysis and statistical approach

Statistical design: As a first data underwent tests for normality using Shapiro-Wilk test. We observed that neither OSA-related measures nor sleep scoring parameters met normality criterion. Therefore, unless specified otherwise, all statistical tests were non-parametric. We conducted independent non-parametric tests (Wilcoxon rank sum test) controlling for multiple comparisons using false-discovery rate (FDR) correction at $p = 0.05$. In cases where recorded measures are independent of one another, we used a non-parametric variant of repeated-measures analysis of variance (rmANOVA), the Friedman test, to test them collectively. Analyses were carried out

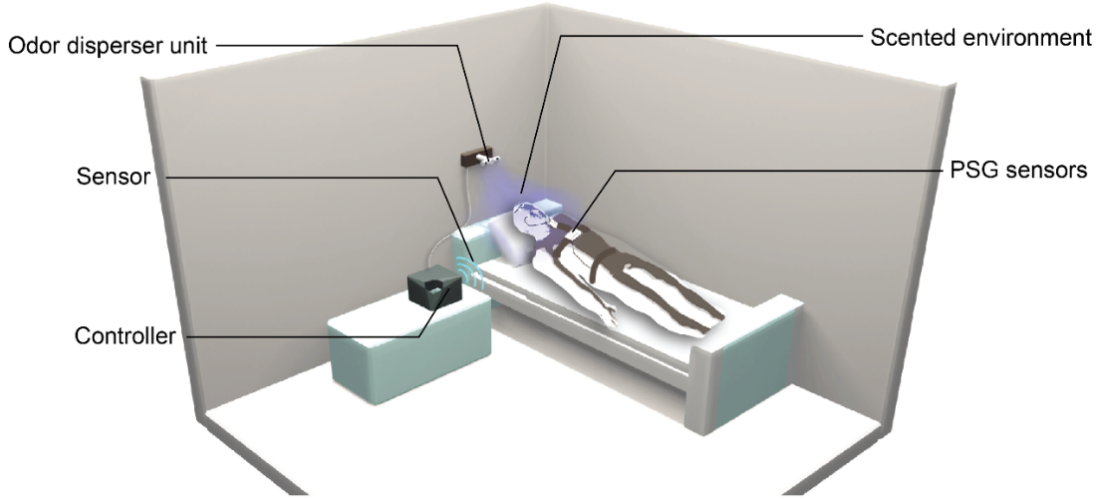
using custom code in MATLAB R2018a (MathWorks, Natick, MA) and JASP 2019 version 0.16.4.

Generally, the analyses described in this study were conducted using two-tailed tests, unless explicitly stated otherwise. Regarding the effects of olfactory stimulation on OSA, here we set out to conduct this study with a clear hypothesis in mind, as stated in the clinical trial registration (NCT04609618) about a unidirectional effect by which olfactory stimulation will relieve apnea related symptomatic measures (AHI, ODI). Therefore, we tested these two specific hypotheses about decreases in AHI and ODI using one-tailed tests.

Additionally, we included Bayesian non-parametric paired tests where appropriate, in order to provide additional information regarding the evidence in favor of the null hypothesis [50]. Specifically, we compared the probability that odor presentation had no effect on a parameter (H0), to the alternate hypothesis that this parameter will change during the 'Odor' condition (H1) with a Cauchy prior of 0.707 [51]. In line with the frequentist hypothesis testing described above, Bayesian tests of effects of olfactory stimulation on OSA also relied on one-sided assumptions. All Bayesian statistical analyses were conducted in JASP 2019 version 0.16.4.

Figure 1

a


Odor disperser unit
Scented environment
Sensor
PSG sensors
Controller

b

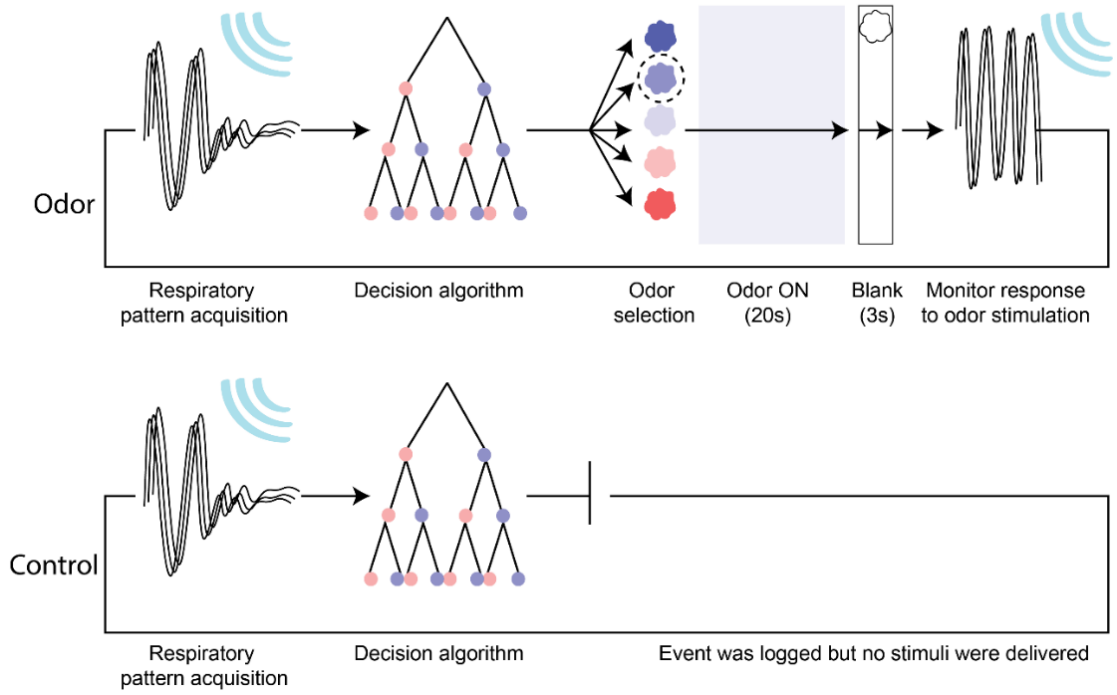

Odor
Respiratory pattern acquisition
Decision algorithm
Odor selection
Odor ON (20s)
Blank (3s)
Monitor response to odor stimulation
Control
Respiratory pattern acquisition
Decision algorithm
Event was logged but no stimuli were delivered

Figure 1:

(a) *Illustration of the experimental room. Patients spent two nights undergoing standard PSG. The olfactometer's controller unit monitored and analyzed respiratory patterns using a contactless radio wave emitter. Olfactory stimulation was delivered via a wall-mounted disperser unit above the patient's head.*

(b) *Olfactory stimulation procedure. Top: in the 'Odor' condition respiratory patterns were continuously monitored and served as input to the decision algorithm. If characteristics of apnea-hypopnea patterns were met, the olfactometer dispersed one of five odorants selected at random for 20 seconds. Next, a 3-second burst of clean air (Blank) were presented. Finally, the olfactometer again monitored respiratory patterns for the next bout of this decision cycle. Bottom: in the 'Control' condition respiratory patterns were continuously monitored and served as input to the decision algorithm in order to log respiratory events, however no odors were dispersed. Note that contrary to the illustration, wireless monitoring did not stop during odor/blank delivery but persisted during odor presentation.*

RESULTS

Olfactory stimulation during sleep reduced apnea-hypopnea events in OSA patients

First, we set out to test the hypothesis that olfactory stimulation during sleep decreased OSA symptoms. We observed that in nights in which olfactory stimulation was delivered, AHI indices were significantly reduced (AHI 'Odor': 22.16 ± 16.2, AHI 'Control': 31.65 ± 17.4, Wilcoxon one-tailed non-parametric test: $z = -2.05$, $p = 0.02$, $BF_{10} = 115.85$), reflecting an average decrease of 31.3% in the number of events (Fig. 2a).

In a follow up analysis, we examined the influence of olfactory stimulation during sleep on each component of the AHI separately (Apnea Index (AI) including obstructive/central apnea events and the Hypopnea Index (HI) including a reduction > 30% in airflow). Odor perception is directly linked to the amount of air entering the nostrils [52] and thus we hypothesized that olfactory stimulation will have a greater influence on hypopnea events in comparison to apnea events. A non-parametric repeated measures ANOVA (Friedman test) with conditions of 'Stimulation (Odor/Control), and 'Index' (Apnea Index/Hypopnea Index) uncovered a main effect of 'Stimulation' in which 'Odor' nights were associated with lower AI and HI indices, ($F = 3.56$, Kendall's $W = -18.65$, $p = 0.021$), and a main effect of 'Index' in which hypopneas were more frequent than apneas ($F = 6.7$, Kendall's $W = -20.78$, $p < 0.001$), in line with previous findings [53]. However, in contrast to our hypothesis there was no interaction between 'Stimulation' and 'Index' (computed on the difference between (Odor - Control) per index, non-parametric test: $z = -0.052$, $p = 0.85$, $BF_{10} = 2.49$). Post hoc planned comparisons revealed that olfactory stimulation reduced HI (HI 'Odor': 12.85 ± 8.33, HI 'Control': 17.64 ± 6.56, Wilcoxon one-tailed non-parametric test: $z = -2.1$, $p = 0.02$, $BF_{10} = 2.39$, Fig. 2b), but not AI (AI 'Odor': 9.31 ± 10.1, AI 'Control': 14.01 ± 17.6, Wilcoxon one-tailed non-parametric test: $z = -0.64$, $p = 0.26$, $BF_{10} = 1.56$, Fig. 2c). Together, these findings demonstrate that transient odor stimulation during sleep decrease AHI in OSA patients.

Following odor presentation, patients' OSA severity changed as follows: Out of the nine patients with moderate OSA, one (11.1%) patient improved to normal AHI (< 5 events / hour), six (66.6%) improved to mild OSA classification and two (22.2%) remained in the moderate category. Out of seven patients with severe OSA, following olfactory stimulation, one (12.5%) patient improved to mild OSA, two (25%) improved to moderate OSA and five (62.5%) remained in the severe OSA category (Fig. 2d). We observed between-patient variability in the reduction in AHI (Fig. 2e) and therefore asked whether this variability is linked to baseline symptoms severity

(i.e., AHI in ‘Control’). Nevertheless, these two measures were not correlated (Spearman’s $\rho = -0.042$, $p = 0.87$, Fig. 2f).

We next confirmed that the order of conditions had no effect on changes in respiratory measures. We employed the same design, this time modeling session order (‘Visit1/‘Visit 2’) instead of conditions of olfactory stimulation. OSA-related respiratory measures were not affected by session order (AHI: ‘Visit 1: 28.11 ± 19.9, ‘Visit 2: 25.69 ± 14.7, Wilcoxon non-parametric test: $z = -0.17$, $p = 0.86$, $BF_{10} = 0.32$; HI: ‘Visit 1: 15.33 ± 7.67, ‘Visit 2: 15.15 ± 8.10, Wilcoxon non-parametric test: $z = -0.26$, $p = 0.60$, $BF_{10} = 0.25$; AI: ‘Visit 1: 12.78 ± 17.8, ‘Visit 2: 10.54 ± 10.1, Wilcoxon non-parametric test: $z = -0.5$, $p = 0.31$, $BF_{10} = 0.364$), suggesting that the observed reduction in AHI following odor stimulation during sleep is not a results of conditions order.

In line with the improvement in AHI, we observed significant yet statistically marginal reduction in ODI – olfactory stimulation reduced the oxygen desaturation index by 26.9 % (ODI ‘Odor’: 20.63 ± 18.9, ODI ‘Control’: 28.81 ± 22.2, Wilcoxon one-tailed non-parametric test: $z = -1.65$, $p = 0.049$, $BF_{10} = 18.97$, Fig. 2g; ODI: ‘Visit 1: 26.09 ± 23.8, ‘Visit 2: 23.35 ± 17.8, Wilcoxon non-parametric test: $z = -0.03$, $p = 0.97$, $BF_{10} = 0.346$). Altogether, these findings suggest that odor presentation during sleep reduces the severity of OSA.

Figure 2

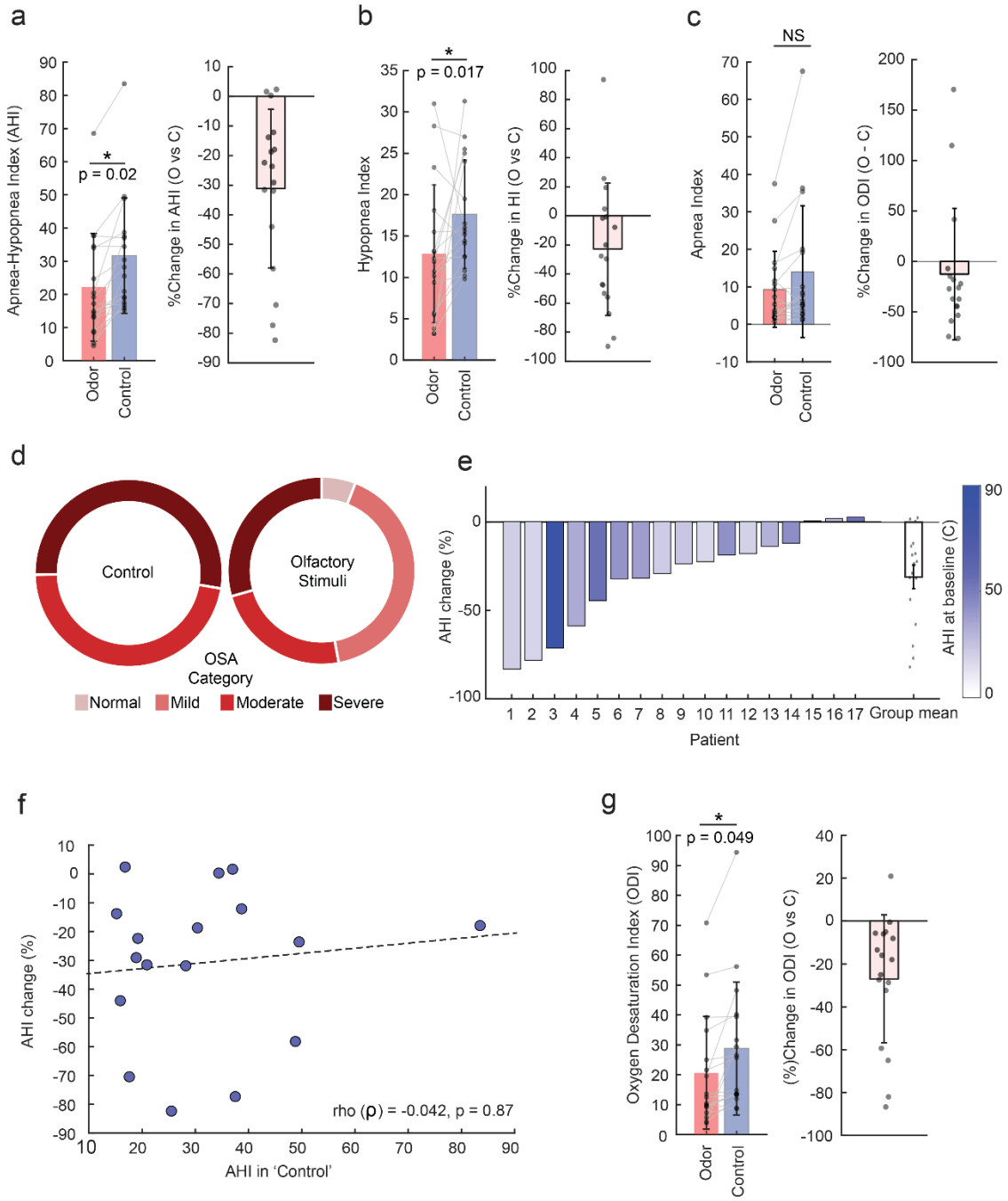

a
Apnea-Hypopnea Index (AHI)
*
p = 0.02
Odor
Control
%Change in AHI (O vs C)
b
Hypopnea Index
*
p = 0.017
Odor
Control
%Change in HI (O vs C)
c
Apnea Index
NS
Odor
Control
%Change in ODI (O - C)
d
Control
Olfactory Stimuli
OSA Category
Normal
Mild
Moderate
Severe
e
AHI change (%)
AHI at baseline (C)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 Group mean
Patient
f
AHI change (%)
rho (ρ) = -0.042, p = 0.87
AHI in 'Control'
g
Oxygen Desaturation Index (ODI)
*
p = 0.049
Odor
Control
(%)Change in ODI (O vs C)

Figure 2:

(a) *Left: Bar graphs depicting group mean of Apnea-Hypopnea Index (AHI) scores for 'Odor' and 'Control' nights (red and blue respectively). Points represent participants (N=17), with cross-condition lines overlaid to aid in visualization of within-subject effects. Error bars are SEM. * $p < 0.05$, NS not significant. Right: A bar graph for mean group percent change in AHI scores (['Odor' - 'Control']). Points represent participants. Error bars are SEM.*

(b) *Same as* ***(a)*** *but for the effect of olfactory stimulation on measures of Hypopnea Index (HI).*

(c) *Same as* ***(a)*** *but for the effect of olfactory stimulation on measures of Apnea Index (AI).*

(d) *Categorical change in apnea severity classification following olfactory stimulation during sleep (N=17). A breakdown of OSA classification in the 'Control' night (left) versus when 'Olfactory stimuli' were presented (right). Color intensity signifies OSA severity categories ranging from normal (light red) to severe (dark red).*

(e) *Bars depicting individual (%)change of Apnea-Hypopnea Index in 'Odor' nights compared to 'Control' nights. Color map denotes OSA severity according baseline AHI measured in the 'Control' night. Rightmost bar depicts (%)change of the group mean. Points represent participants (N=17). Error bars are SEM.*

(f) *Scatter plot of AHI change (%) in the 'Odor' condition as a function of AHI in 'Control'. Each data point is a patient (N = 17). Trend line is Spearman correlation, correlation coefficient and p value displayed in the figure.*

(g) *Same as* ***(a)*** *but for the effect of olfactory stimulation on measures of Oxygen Desaturation Index (ODI).*

Olfactory stimulation during sleep did not alter apneas-hypopneas duration in OSA patients

Next, we tested whether olfactory stimulation during sleep reduced the duration of apnea-hypopnea events. We relied on the duration of apnea-hypopnea events as logged by the PSG equipment and therefore the following analysis assessed the effect of olfactory stimulation only on apnea-hypopnea detected by the PSG. First, we examined all five odors combined and found no difference in event duration between 'Odor' and 'Control' nights ('Odor': 21.94 ± 6.34 s, 'Control': 22.28 ± 3.89 s, Wilcoxon one-tailed non-parametric test: $z = 0.69$, $p = 0.75$, $BF_{10} = 0.26$). To examine the effect of respiration-based transient odor stimulation we compared the duration of apnea-hypopnea events in the 'Odor' nights, that were conjugated with odor stimulation (i.e., the respiratory event which was the trigger for odor delivery) and events that were not conjugated with odor stimulation. We found no difference in apnea-hypopnea events duration between the two conditions ('Conjunction: 22.36 ± 7.85 s, 'Non-Conjunction': 22.66 ± 7.22 s, Wilcoxon one-tailed non-parametric test: $z = -0.14$, $p = 0.44$, $BF_{10} = 0.34$). Then, we examined the influence of each odor separately. Over the course of the night olfactory stimulation was delivered using a fixed repertoire of five odor mixtures, primarily in order to reduce potential sensory habituation to recurrent exposures (Table 3). To test whether some odors were consistently more effective than others in reducing OSA symptoms we sampled the duration of apnea-hypopnea events that were conjugated with each odor type. Normalized apnea-hypopnea events duration (within patient using z-score, see methods) showed no consistent effect of odorant type at the group level (rmANOVA $F(4,64) = 0.56$, $p = 0.67$). Given known individual variability in odor perception [54,55], we repeated the analysis in the single-patient level. Again, we were not able to detect significant differences in conjugated apnea-hypopnea events as a function of odor type. These findings imply that odor stimulation during sleep does not reduce the duration of apnea-hypopnea events.

Olfactory stimulation did not alter sleep structure

We then asked whether olfactory stimulation altered sleep structure, quantified as percent of time in bed (%TIB) spent in wakefulness and each sleep stage. Across all sleep stages (Wake / REM / N1 / N2 / N3), %TIB did not change between 'Odor' and 'Control' (all $p > 0.44$, all $BF_{01} > 2.9$). In addition, as expected we observed that on the first night in the sleep lab, regardless of whether odors were presented, the %TIB spent at wake was significantly higher (%TIB at wake: 'Visit 1': 14.58 ± 9.43, 'Visit 2': 10.00 ± 5.69, Wilcoxon non-parametric test: $z = 1.96$, $p = 0.049$, $BF_{10} = 6.45$). Moreover, sleep efficiency was marginally lower on the first night (sleep efficiency: 'Visit 1': 85.36 ± 9.5, 'Visit 2': 89.59 ± 5.76, Wilcoxon non-parametric test: $z = -1.76$, $p = 0.079$, $BF_{10} = 5.79$). Both these factors can be attributed to 'first night' effects due to sleeping in the unfamiliar lab setting [56]. In line with previous studies [19–23], these findings demonstrate that odor presentation during sleep does not disturb sleep or alter sleep architecture significantly.

DISCUSSION

In this study, we sought to determine whether olfactory stimulation during sleep can alleviate sleep apnea symptoms. To address this question we capitalized on the unique neurocircuitry of the olfactory system – unlike other sensory modalities, olfactory information projects from sensory regions to the olfactory cortex without a thalamic relay [57]. This divergence in neural architecture is thought to underlie the ability of odors to exert physiological and neurological effects without inducing arousal [23,31].

Our main finding is that transient olfactory stimulation during sleep was associated with a pronounced reduction in patients' Apnea-Hypopnea Index (AHI). Out of a cohort of 17 patients,

14 patients (82%) exhibited a reduction in AHI while the remaining three (18%) showed very subtle increases (all < 1 AHI). In other words, olfactory stimulation was beneficial for the majority of patients, and when not beneficial, it did not alter their OSA symptoms severity as measured by AHI. Interestingly, AHI reduction by odor stimulation was not related to baseline OSA symptoms severity in this cohort (15<AHI<83 at baseline). OSA severity is linked to olfactory dysfunction [58,59] yet the exact pathophysiological reasons are unclear [60]. Therefore, one would expect olfactory dysfunction to moderate effects in severe patients in our cohort, yet such a trend was not observed. During screening patients reported subjectively normal olfaction but did not undergo an objective evaluation (e.g., 'Sniffin' Sticks). Follow-up studies should dwell on this point if to delineate the precise relationship between olfactory abilities and the influence of olfactory stimulation during sleep on OSA systematically.

To our knowledge, this is the first study to report beneficial effects of olfactory stimulation during sleep on OSA in adults. Our results complement several lines of evidence from research conducted on neonatal apnea of prematurity [36,37] (but see [61] for opposite results) who reported ambient exposure to the odorant vanillin reduced apnea symptomatology. Curiously, the authors alluded these beneficial effects to pharmacological and neurophysiological features of vanillin, which cannot be universally applied to a wider repertoire of odors.

One central aspect in which our study diverges from previous studies employing olfactory stimulation in sleep is the transient, ad-hoc, delivery of a rotating selection of odors. The olfactometry device used in this experiment monitored breathing patterns using radio impulses independently, and in tandem with PSG equipment and presented odors according to internal machine-learning algorithms trained to detect the onset of apnea-hypopnea events. Compared with the manually-validated PSG recording, the olfactometer detected about 46% of the PSG detected events. Notably, even though only about half of the apnea-hypopnea events were

detected, we observed a reduction of over 30% in AHI. This imply that higher detection rates may results in greater reduction in AHI. In parallel, it is possible that the olfactometer only detected events which were unobservable by PSG sensors, but we have no reference to those, as we only compared the PSG records to corresponding olfactometry logs.

Arguably, this method of transient odor delivery led to less sensory habituation, rendering it advantageous compared to methods of constant passive exposure, which have been the standard stimulation method in most studies focusing on olfactory exposure and sleep quality [62,63]. Recently there has been an upsurge in the incorporation of technological know-how such as conditionally-triggered olfactometry [35,64], miniaturization [65], and on-the-fly processing with machine learning (as done here) into this millennia-old practice, a trend that allows for more intricate and precise experimental designs.

Olfactory stimulation did not alter sleep structure. The main concern, namely that odor stimulation might induce arousals, did not materialize as wakefulness-related measurements were unaffected by olfactory stimulation. In line with this claim, we did not observe olfactory-induced improvement in parameters of sleep quality (e.g., %SWS, sleep efficiency). This finding does not align with several previous studies supporting the sleep-promoting attributes of odors. A plausible explanation for this discrepancy could stem from reduced proportion of SWS in OSA patients at baseline [66,67]. Alternatively, it is also possible that the measure of %TIB was not sensitive enough to capture subtle changes in sleep structure.

Despite presenting patients with five different odorants, odor identity did not have a direct effect on the duration of ensuing apnea-hypopnea events. Further, across the cohort no single odor type emerged as more effective than the others in the repertoire. This observation is in line with previous studies showing that during sleep odor identity often had no clear effect [23,31,68]. Notably,

in the study by Perl and Arzi et al., electrophysiological effects were comparable whether pleasant rose or pungent rotten eggs odorants were presented [69]. In contrast, a study by Goel et al. established a link between perceptual attributes of an odorant at wake and its sleep promoting effects [63]. All in all, although olfactory perception at wake often varies across participants and odorants, we cannot claim that in this study such variability extended into sleep. We note however, that despite being drawn at random, the number of presentations per odor varied across patients considerably, and was not equated within patients. A systematic design focused at this specific question is in order, if to tackle this question directly. We propose that each odor could be tested at different night or alternatively be administered in a clustered manner to better suit testing odor-specific effects.

The neurological mechanisms at play in OSA onset are not well understood and the traditional segregation between its mechanical and neurological causes is less clear than previously assumed. Several characteristics of OSA suggest involvement of the central nervous system in the genesis or maintenance of the syndrome: apneas are often mixed in type, beginning with a central component and followed by an obstructive period [70]. For example, obstructed breaths in OSA are frequently preceded by short breathing pauses, apparently of central origin [7]. These observations warrant a neuro-centric approach for the treat of sleep apnea. What mechanism may mediate the effects of olfactory stimulation on respiratory disorder? We propose that a mechanism by which breathing is reinstated through the aspiration reflex; Nasopharyngeal stimulation was shown to stop apnea and restore spontaneous breathing in rodents and cats [71,72], most likely through medullary nuclei of the pre-Bötzinger complex which act as respiratory pace-makers [73]. These forms of salient nasopharyngeal stimulation (trigeminal, electrical or mechanical stimulation) however, also induce arousal, rendering them irrelevant for OSA treatment. If olfactory stimulation can be regarded as a low-amplitude form of nasopharyngeal stimulation, one may

speculate that odors may lead to the same triggering of the aspiration reflex without inducing arousal. In our study odors varied in their levels of trigeminality, with the majority of odors possessing at least some degree of trigeminality [18,74] which is speculated to be the principal element of the nasopharyngeal stimulation. The literature is undecided regarding the extent of trigeminality odors must possess (along with considerations of concentration) to induce arousal from sleep [20,21,75]. Therefore, here we deliberately tested some odors with pronounced trigeminal perception (e.g., eucalyptus).

Finally, we would like to highlight several limitations of our study; First, due to multiple exclusions, our sample size consisted of 17 patients, which limits the generalizability of the observed effects and may have obscured additional effects due to low statistical power. Second, our results should be replicated in a more longitudinal design involving multiple nights per condition in order to test gradual cumulative effects and reduce natural between-night variability in OSA measures which is known to introduce noise.

In conclusion, the high prevalence of OSA combined with current insufficient solutions such as low adherence rates to CPAP warrants the search for alternative treatments a high priority. Our results suggest that olfactory stimulation during sleep is a viable such alternative, prompting continued research on this front.

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Disclosure Statement

OP is a paid consultant at AppScent. AA is a non-paid consultant at AppScent. Both OP and AA received the PSG clinical data only once data collection was terminated and were not involved in the conception of the experiment.

Table 1: Breakdown of exclusion criteria

Exclusion Criteria	**N (%)**
AHI < 15 in the control condition	7 (21.87%)
Less than 4 hours sleep time	3 (9.37%)
Missing night in the lab	2 (6.25%)
AHI < 15 in control condition + Missing night in the lab	1 (3.12%)
Less than 4 hours sleep time + AHI < 15 in the control condition	1 (3.12%)
Asthma	1 (3.12%)
Patients included in the study	17 (53.12%)
Total	32 (100%)

Table 1: Exclusion criteria and their occurrence in the recruited cohort.

Table 2: Demographic variables for patient cohort (N = 17)

Patient	Age (years)	Sex	Weight (kg)	Height (cm)	BMI	Medical history
1	47.4	Female	64	169	26.4	
2	61.5	Female	84	158	40.8	Metabolic, Genitourinary, Psychiatric
3	55.2	Male	87	167	36.9	Cardiovascular, Gastrointestinal
4	47.5	Male	90	170	36.5	
5	60.8	Male	89	172	35.0	Respiratory, Metabolic
6	34.4	Male	83	172	32.7	
7	55.4	Male	77	173	29.8	
8	45.5	Male	90	175	33.8	
9	36.7	Male	78	187	24.2	Metabolic
10	44.9	Male	90	178	32.2	Metabolic
11	66.5	Male	88	170	35.7	Metabolic
12	44.9	Male	73	172	28.7	
13	30.3	Male	80	180	27.8	
14	52.1	Female	82.1	162	37.6	Genitourinary
15	43.1	Male	74	172	29.1	Metabolic, Psychiatric
16	65.2	Female	69	150	37.6	Metabolic, Genitourinary, Allergic
17	45.0	Male	91	168	38.1	Metabolic
Average	**49.19**		**81.71**	**170.29**	**33.11**	
STD	**10.18**		**7.93**	**8.13**	**4.61**	
Median	**47.4**		**83.0**	**172.0**	**33.8**	
Minimum	**30.3**		**64.0**	**150.0**	**24.2**	
Maximum	**66.5**		**91.0**	**187.0**	**40.8**	
95% C.I	**{43.8, 54.59}**		**{77.6, 85.92}**	**{165.99, 174.6}**	**{26.51, 30.13}**	

Table 2: Demographics and medical history of the patient cohort. Patient data are reported individually as well as descriptive statistical values of the cohort. BMI, body-mass index; STD, standard deviation.

Table 3: Breakdown of odor presentations

Patient	Odor1 O	Odor2 E	Odor3 L	Odor4 F	Odor5 G	Total conj.	Total non-conj.	Grand total
1	5	4	4	2	3	**1**	**17**	**18**
2	31	31	30	31	29	**27**	**125**	**152**
3	62	65	64	59	60	**207**	**103**	**310**
4	39	38	37	40	36	**62**	**128**	**190**
5	34	29	27	29	31	**101**	**49**	**150**
6	20	20	18	23	22	**44**	**59**	**103**
7	36	31	31	28	33	**55**	**104**	**159**
8	26	25	26	26	23	**18**	**108**	**126**
9	21	18	20	20	18	**18**	**79**	**97**
10	18	16	16	20	17	**22**	**65**	**87**
11	23	21	22	18	23	**5**	**102**	**107**
12	33	27	30	27	25	**18**	**124**	**142**
13	20	15	19	19	14	**34**	**53**	**87**
14	18	14	12	13	13	**13**	**57**	**70**
15	9	7	8	6	6	**2**	**34**	**36**
16	15	4	13	8	6	**3**	**43**	**46**
17	17	16	15	16	20	**17**	**67**	**84**

Table 3: Number of odor presentations per patient. A breakdown of number of olfactory stimulation epochs. Data are reported per patient (rows) and per odorant (columns). Right-hand side columns report the total number of presentations for odor presentations which were conjugated (conj.) and non-conjugated (non-conj.) to apnea-hypopnea events respectively, as logged by the PSG. Odorants: O = orange, E = eucalyptus, L = lavender, F = frankincense-cinnamon, G = geranium.

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