Multi-channel portable odor delivery device for self-administered and rapid smell testing

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Title: ‘Generating Olfactory Experiences’. Description: System and a method of generating olfactory experiences. Application numbers: US 2021/346562 A1 (pending), EP 3784298 A1 (pending); Applicant: University of Sussex. Inventors: Emanuela Maggioni and Marianna Obrist. Title: ‘Adaptive Smell Delivery System’ Description: A smell delivery device with a delivery channel to produce olfactory output. Application numbers: GB 2600142 A (pending), US 2024/0000368 (pending), EP 4231898 A1 (pending), JP 2023-549141 (pending). Applicant: OWidgets Ltd. Inventors: Emanuela Maggioni, Richard Hopper, Marianna Obrist and Florin Udrea.

Multi-channel portable odor delivery device for self-administered and rapid smell testing

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Abstract

To improve our understanding of the perception of odors, researchers are often required to undertake experimental procedures with users exposed to multiple odors in a variety of settings, including to diagnose smell loss in clinics and care homes. Existing smell tests are typically administered using multiple sniffing pens manually presented to patients by a highly specialized nurse using a time-consuming and complex testing paradigm. Automated odor delivery devices, such as olfactometer systems, exist but are expensive, bulky and typically lab based, making them difficult to use for "on the ground" odor delivery. We have developed a portable, affordable, odor delivery device that can deliver 24 odors through individual channels with high temporal precision and without cross-contamination. The device allows for the fast, flexible sequencing of odors via digital control using a mobile application and has been experimentally validated in the lab, as well as tested on patients. The novel design provides several unique advantages for investigating olfactory perception and offers the possibility that

users can one day self-administer smell tests in a range of settings, including at home, allowing smell healthcare services to evolve and become part of a routine practice and self-care culture.

Keywords: Olfaction, Odor, Scent, Smell, Olfactometer, Testing, Device

1 Introduction

The sense of smell is one of the five main senses that links us to the world around us and plays a vital role in our health and well-being. Just like with other senses, any disruption or loss to our ability to smell (i.e., smell dysfunction), can have a debilitating impact on our quality of life, e.g., affecting our emotional, cognitive, and / or mental health [1, 2]. For example, smell dysfunction can reduce social confidence through the inability to reliably assess personal hygiene state and carries an increased risk to well-being and personal safety (e.g. the inability to judge food safety, detect fire hazards, leaking gas, etc.) [3]. Our senses can also affect each other, e.g., smell and taste, where a loss of smell usually equates to a loss of taste [4], leading to a reduced ability to enjoy food that can have a negative effect on nutrition, and / or the immune system [5].

Smell dysfunction is also an important biomarker for various neurological diseases [6]. For example, it is well established that olfactory impairment predicts incident mild cognitive impairment and progression to Alzheimer's disease [7, 8]. With life expectancy rising, there are an increasing number of age-related neurodegenerative diseases (like Alzheimer's [7] or Parkinson's [9]), contributing to increased pressure on healthcare providers. There is therefore a growing need for innovation to facilitate the introduction of personalized and stratified medicine, with a focus on the early diagnosis of disease, prevention rather than cure, care closer to the home and continuous health monitoring, rather than periodic sampling [3, 10]. This calls for a more engaged public with higher levels of awareness for smell health and care that will assist in relieving the financial pressure of such situations by adopting novel diagnostic technology and remaining healthier and independent for longer [11].

Tests to evaluate our sense of smell are complicated by a number of factors, including the high dimensionality of the olfactory stimulus space and the large dynamic range of human smell receptors. Overcoming these challenges often requires testing with large numbers of odorants of different types and dilutions [12] to adequately cover even a portion of the olfactory stimulus space. Smell tests also need to be rapid and easy to administer, without sacrificing the quality of clinically important data, such as olfactory threshold values [13].

By analogy to hearing tests, which measure the lowest perceived intensity of a sound, olfactory threshold tests measure the lowest perceived concentration of an odor. Existing threshold tests use multiple felt-tip pens filled with serial odorant dilutions [14] which are manually presented to the patient by a highly specialized nurse using time-consuming and complex testing paradigm [15]. Although the olfactory threshold test is a clinically essential component of smell evaluation, this test is rarely performed in clinical settings because of its complex and lengthy procedure [16].

Olfactometers are widely used throughout olfactory research, enabling the automated delivery of temporally controlled flows of odor to subjects. Olfactometer systems typically have a number of common components, including a filtered 'clean air' supply delivered by a pump from the environment [17] or from a gas cylinder [18]; one or more temporally activated odor sources [19]; delivery channels; and a method of spatially directing odor to the user, such as through a face mask [18], [20] or nasal attachment [21]. A summary of different approaches for odor delivery is given in Table 2.

Odorized air can be generated in a number of ways, including through the use of bottles containing liquid odorant [17]; gas sample bags [22], gas filled syringes [23]; and active thermal evaporation of liquid odorant using a heated plate [24].

To determine a patient's odor threshold, the olfactometer system must be able to generate a range of odor concentrations. The odor concentration can be controlled by diluting the odor stream with clean air [22], however, gaseous dilution typically requires the use of proportional valves to control the dilution ratio which can add cost and complexity to the system. In addition, the use of a common mixing chamber can lead to cross-contamination between odors, unless the system is carefully cleaned and flushed out between tests [25]. An alternative approach for varying odor concentration which avoids cross-contamination and expense is the use of multiple channels with serially diluted odorants [19]. The airflow through the individual odor channels can be conveniently controlled using an array of solenoid valves and associated electronic control circuitry.

Given the high number of sub-components used in typical olfactometer systems, including pumps, temperature controlled odorant reservoirs, tubing, valves and mass flow controllers, olfactometer systems are generally high cost, bulky and limited to lab based environments. Some attempts have been made to develop miniaturized odor delivery devices, for example, [18] reported on a miniaturized single channel odor delivery device that uses interchangeable cartridges filled with odour vapor. Miniaturized odor delivery devices have also been commercially developed, including by Aromajoin Corp. (Japan), whose system employs replaceable odourant cartridges activated by piezoelectric air pumps. OVR Tech LLC (US) have also developed a wearable system based on a VR headset fitted with odorant cartridges activated by a piezoelectric actuation. However, such low cost miniaturized devices are aimed at the entertainment market and often have compromised performance, including limited odor flow, poor control of odor intensity, poor directivity of the odour stream to the user, poor temporal resolution, contamination issues between odor channels and limited flexibility, e.g., due to the use of proprietary odorant cartridges.

There is therefore a need to create compact systems for odor delivery to enable smell tests that are time efficient (able to deliver tens to hundreds of odorants per test session) and flexible to allow the odorant selection to be easily tailored to suit the needs of the experiment.

Here, we describe a portable multi-channel odor delivery device capable of efficient and flexible odor delivery for research applications in a variety of settings. The novel digitally controlled device uses interchangeable odorant cartridges (24-channels), which can be prepared during the course of an experiment, such as that demonstrated for smell testing.

Table 1 Odor delivery system approaches.

Author	Year	Ref	Odor source	Control method	Outlet	Channels
J. N. Lundström	2010	[17]	Odorant bottle	Solenoid controlled odor lines with flow control and dilution.	Nose piece	9
S. D. Burton	2019	[19]	Odorant bottle	Solenoid controlled odor lines. Open air mixing with carrier stream.	Nose piece	12
P. Risso	2018	[20]	Odorant reservoir	Fan coupled to rotatable odor reservoirs.	Outlet port	8
C. M. Owen	2002	[26]	Odor filled syringes	Motorised syringes.	Face mask	1
A-K Bestgena	2015	[27]	Odorant bottles	Solenoid controlled odor lines.	Nose piece	12
V. Nieminen	2018	[24]	Heated liquid odorant	Solenoid controlled odor lines.	Outlet port	3
J.J.R. Feddes	2001	[22]	Sample bags	Solenoid controlled odor lines with flow control and dilution.	Outlet port	3
M. Vigourouxa	2005	[18]	Odorant bottle	Odor injection into carrier stream.	Face mask	1

2 Device description

The odor delivery device presented here utilises components common to most olfactometer systems, including a clean air supply, solenoid valves for directing airflow to the selected odor source and a method to deliver the odor to the user. This device is developed by OWidgets Ltd., a University spin-out, and of the back of international scientific collaborations, including the effort to innovate towards a new odor delivery method for smell testing. A cutaway image showing the system components and a pneumatic diagram are shown in Fig. 1(a) and Fig. 1(b), respectively.

For odor transport, the device draws air from the environment using a diaphragm pump (Parker, BTX Connect) with a maximum flowrate of 6 L/min. To remove traces of organic compounds, the air is first filtered using an activated carbon filter (Festo, MS4/D-MINI-LFX). The filtered 'clean air' is then piped to an aluminium manifold which helps to smooth the airflow which is distributed to a bank of 24 solenoid valves (Zanty, SDF-0626L) that can be individually activated to direct airflow into separate odor reservoirs. The airflow rate can be adjusted over a range 2 L/min - 8 L/min using a flow regulator (Festo, GRLA-M5-QS-4-D).

Liquid odorants are contained on sponge materials within 24 odor reservoirs which are housed in a removable aluminium cartridge. The odorant cartridge is mounted on metal posts and is clamped into place using a pair of latches to form an airtight seal, permitting flexible deployment for tests. The large number of channels permits the use of odorants of different concentrations and types. The small headspace of the odour reservoirs allows them to quickly fill with saturated vapour. Upon activation of airflow into an odor reservoir, saturated odor vapour is picked up and piped to an outlet

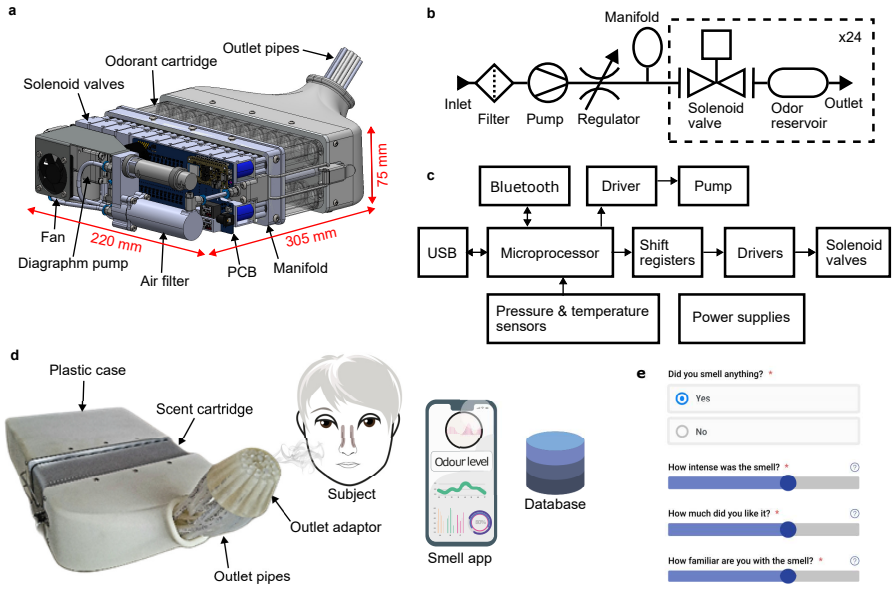

Fig. 1 | **System description. a**, Cutaway CAD image showing the key components of the 24-channel odor delivery device, including the air filter, diaphragm pump, solenoid valves and odorant cartridge. **b**, Pneumatic diagram illustrating the airflow through the components of the odor delivery device. Air from the surrounding environment is filtered, pumped and channelled by a bank of 24 solenoid valves to an odor reservoir where it is odorized before reaching an outlet. **c**, A system diagram of the electronic control circuitry. A Bluetooth / microprocessor module (Raytac, MDBT50Q-1MV2) is used for system control and communication. Digital lines are interfaced to higher voltage (12 V) drivers for activation of the solenoid valves and diaphragm pump. A pressure sensor is used for diagnostic tests during system operation. **d**, An image of the assembled device and its interaction with the user and mobile application. The device is housed in a 3D printed plastic case and contains an odorant cartridge which slides onto fixing posts and is screwed into place within the assembly. Individual outlet pipes are held using an adapter. A mobile app is used for system control and for recording perceptual data from users (stored on a cloud database). **e**, A screenshot showing the mobile app used for system control and recording perceptual data from users of the smell delivery device. After each odor exposure, users are asked a series of questions including inviting them to rate the smell intensity, character and familiarity.

channel through Teflon pipes. The use of individual outlet pipes channels avoids cross contamination between odors. The odor flow from the pipes is directed toward a focal point 10 cm always from the outlet using a resin printed adaptor shown in Fig. 1(d).

The functional blocks of the device's electronic control circuitry are shown in Fig. 1(c). System control and communication are enabled by a CPU and Bluetooth module (Raytac, MDBT50Q-1MV2) on an Adafruit Feather nRF52840 Express board, integrating a Low Energy Bluetooth 2.4 GHz transceiver and an ARM Cortex-M4 CPU which acts as a low power controller for the rest of the system.

The solenoid valves are controlled by a serial digital output from the CPU which is routed to shift registers to generate a set of 24 parallel digital outputs which are used to switch higher voltage (12 V) MOSFET driver circuitry. The diaphragm pump is controlled using a pulse-width-modulated (PWM) signal from the CPU and is driven using similar driver circuitry, permitting electronic control of the airflow.

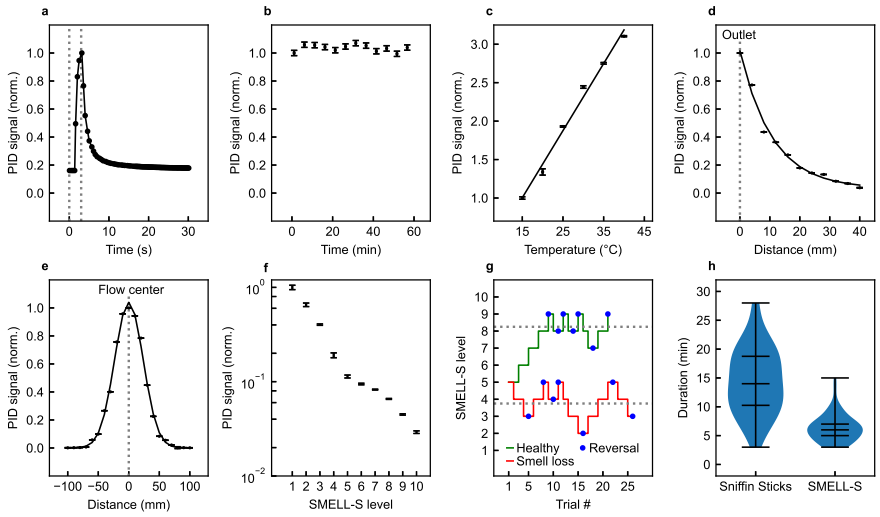

Fig. 2 | **System performance. a**, Transient response of the photo ionization detector (PID) to an odor exposure generated by the odor delivery device with a 3 s activation time (activation times indicated by the dotted lines). **b**, Temporal stability of the odor intensity generated by the odor delivery device over a 1 hour time window with 3 s activation times. **c**, Thermal response, showing the variation in measured odor intensity from the odor delivery device with ambient temperature. **d**, Spatial distribution of odor intensity, measured over a distance of 40 mm from the outlet of the odor delivery device, in the direction of odor flow. **e**, Spatial distribution of odor intensity across the path of odour flow, measured at a distance of 100 mm from the outlet of the odor delivery device. **f**, Measured odor intensity for the SMELL-S odour stimuli. **g**, An example of a subject's performance during the SMELL-S test, for a patient with smell loss treated at the Geneva University Hospital (red line) and a subject with an intact sense of smell (green line). We used an adaptive staircase threshold paradigm to measure olfactory threshold. The task is becoming more and more difficult as the level is approaching 10. A reversal occurs when the direction in which the concentration is changed reverses (blue dots). The score is defined as the average of the last four reversals (grey dotted lines). **h**, Violin plots showing the duration's for the Sniffin' Sticks and SMELL-S threshold tests.

Auxiliary components of the electronic circuitry include a pressure sensor (Freescale, MPX 53GP) for monitoring the internal air pressure of the system and a temperature and humidity sensor (Sensirion, SHT21S) for environmental monitoring. Power to the different sub-modules (3.3 V / 5 V / 12 V rails) is provided by switching regulators from Murata.

The Bluetooth interface permits mobile control and integration of the system into the Internet of Things (IoT). To facilitate this, a mobile app has been developed for control using JavaScript which runs on an Android platform. The app can be used for smell testing applications and allows users to easily trigger the odour delivery using a graphical interface and record perceptual feedback. A screenshot of the app is shown in Fig. 1(d). After an odor delivery has been triggered, the app presents user with a questionnaire, allowing them to record their perceptions of an odor stimuli. User data recorded during each training session is stored on a cloud server for subsequent analysis.

At current prices, the cost of construction of the odor delivery device totals $2,140, with each odorant tested costing an additional few dollars in disposables (i.e., for the odorant and sponge absorber). The cost of the device is expected to fall significantly if the unit is fabricated in volume. The specifications of the device are shown in Table 2.

Table 2 Odor delivery device specifications.

Parameter	Value
Number of odor channels	24
Simultaneous active channels	3
Maximum airflow rate	6 L/min
Outlet type	4 mm pipe
Odor reservoir size	46 mm x 14 mm x 16 mm
Noise level	$\sim$ 60 dB[1]
Power consumption	15 W[1]
Digital interface	USB / Bluetooth
Dimensions (L×W×H)	305 mm × 220 mm × 75 mm
Weight	3.9 kg

[1]In active mode.

3 Device characterisation

A number of characterization tests were performed on the odor delivery device to assess the repeatability of the odor delivery, temperature stability and the spatial distribution of the odor stream. The odorant used for testing was developed for the SMELL-RS test and is described here [12].

The repeatability of the odor delivery was assessed over an extended time period of operation. To monitor the odor intensity, odor from the outlet adaptor of the device was directed towards a photo-ionisation detector (PID). The PID is extremely sensitive to low levels of organic compounds (¡ 3,000 ppb) and signals from the detector yielded a sharp, pulse like response during the odor activation time, as shown in Fig. 2(a), with the odor intensity decaying to background levels after a time period of around 10 s. However, there is likely to be some time lag in the PID sensor recovery due to the build-up of odor in the detector's internal chamber. For the repeatability test, the delta change in odour intensity was extracted from the raw sensor readings. Normalised PID sensor readings for 3 s odor activation times are shown over a 1 hour time period in Fig. 2(b) in indoor conditions. Over this time period, the odor intensity is relatively stable, with a relative standard deviation in odor intensity of 2.4 %. Temporal variations in odor intensity are likely to be caused by temperature changes, the evaporation of the odorant and air currents.

The temperature stability of the olfactometer system was assessed. For these tests, the device was placed in an environmental oven and the odor intensity was measured using the PID sensor over a range of temperature points (15 °C – 40 °C). With the odorant used for these tests, the odor intensity has a measured temperature coefficient of 5 % / °C, as shown in Fig. 2(c). The temperature stability could be improved by the

addition of temperature controlled odorant reservoirs, at the expense of added cost and complexity. As the human perception of odor is a logarithmic phenomenon, the effect of temperature induced changes on perceived odor intensity is less significant than one might expect. In addition, the system is intended for use in thermally stable lab type conditions.

The spatial distribution of the odor stream generated by the device was also investigated. To enable spatial measurements of the odor intensity at different distances from the outlet, the PID gas sensor was mounted onto a motorised stage and positioned at various distances away from the odor source, parallel and across the direction of odor flow. With a simple pipe outlet, the odor intensity drops rapidly in free space, as the odour molecules move and diffuse in all directions away from the outlet, as shown in Fig. 2(d). At 30 mm distance away from the outlet, the odor intensity has dropped to around 10 % of the peak value close to the source. The spatial distribution of the odour stream, looking across the air flow at a distance of 10 cm away from the outlet, is shown in Fig. 2(e). It is clear from these tests that small changes in the position of the subject under test can have a large effect on perceived odour intensity. To ensure repeatability during smell tests, the subject must therefore be accurately aligned with the outlet of the device.

4 Device application to smell testing

To study whether the odor delivery device could decrease the time and human assistance required to administer an olfactory threshold test, we created a customized mobile app to allow for self-administration of the complex testing procedure and used olfactory stimuli from the threshold component of the SMELL-RS concept, called SMELL-S [12].

Olfactory threshold tests use different dilutions of an odourant to measure the lowest perceived concentration, analogous to the way that hearing tests measure the lowest perceived intensity of a sound by exposing users to different sound intensities. The SMELL-S test has 10 odourant dilution levels and the measured odor intensity for each level is shown in Fig. 2(f). We measured the time needed to complete the SMELL-S test with the device and compared it to the time using the Sniffin' Sticks threshold test (current standard). We found that the median time needed to complete the Sniffin' Sticks threshold test was 14 minutes (IQR = 5) versus 6 minutes (IQR = 12) for SMELL-S with the smell delivery device, as shown in Fig. 2(h).

The time saving when deploying SMELL-S can be explained by the absence of human tasks such as capping / uncapping the Sniffin' Sticks, manual reporting of the subject's answer after each trial, and human interaction between tasks. Such tasks can easily introduce human error, limiting the quality of clinical data. Although the clinical performance of SMELL-S will be published elsewhere, we hope that this practical improvement (self-administered, time efficient) will help address an unmet clinical need under the form of a rapid, self-administered, and efficient smell test applicable in different clinical settings around the world.

5 Methods

5.1 Device characterisation

The odorant used to characterize the odor delivery device was developed for the SMELL-RS test (specifically for the Smell-S subtest) and is described here [12]. For characterization, a volume of 300 μL of the liquid odorant was placed on a cellulose sponge carrier using a micro-pipette. The odorant carrier material was placed in the odour reservoir of the device.

Odor intensity was measured using a photo-ionisation detector (MiniPID) from Ion Science. Measurements of stability were positioned at a distance of 25 mm from a 4 mm diameter outlet pipe. Thermal conditions were 25 °C and the odorized airflow rate from the device was 3L / min, measured using a Flusso FLS-110 flow sensor.

For the repeatability test, the odor intensity was measured using the PID gas sensor in an indoor environment over a 1 hour time window at a temperature of 25 °C with an odor activation time of 3 s, repeated every 300 s. The standard deviation (SD) was derived from a set of 50 measurement cycles.

Thermal stability was measured with the device placed in an environmental oven (Thermotron S-1.2 3800). The PID gas sensor was mounted externally to the oven and odorized air fed to it from the olfactometer using 4 mm diameter tubes. Prior to each measurement, the system was left to stabilize for 30 minutes at each temperature point to ensure thermal uniformity.

The spatial distribution of odour intensity was investigated by mounting PID on a motorised stage (Thorlabs, LTS300), having a reach of 300 mm.

5.2 Smell test study design

We performed a test-retest reliability and accuracy study including healthy subjects (n = 37) and patients with various causes of smell loss (n = 31) at Geneva University Hospital. The study involved subjects aged 18 years of age and over, who came to the hospital for two visits spaced approximately one week apart. During the first visit, participants were tested with the current standard test (Sniffin' Sticks) and with SMELL-RS with the smell delivery device. The order of the tests was randomized. On the second visit, the tests were repeated. We recorded the time needed to complete each test. A t-test was used to uncover differences between groups.

5.3 Sniffin' Sticks smell threshold subtest

Subjects were tested with the Sniffin' Sticks test (Burghart, Wedel, Germany), which includes the olfactory threshold, discrimination, and identification sub-tests. The composite score of the three sub-tests was used for the classification of healthy subjects or patients with smell loss [28, 29]. The Sniffin' Sticks threshold subtest uses phenylethyl alcohol (rose-like odor) in pen-like odor dispensing devices. The stimuli's have sixteen dilutions in a geometric series. Three pens were presented in a randomized order, with two containing a solvent and the third the target odorant. The subjects must identify the odor-containing pen. An experimental nurse performed a single-staircase test (with ramped odorant concentrations) with three alternative forced choice procedures

starting at the most difficult level (level 16 out of 16) according to the user manual. Reversal of the staircase is triggered when the odor is correctly identified in two successive trials. The olfactory threshold was defined as the mean of the last four of seven staircase reversals.

5.4 SMELL-S smell threshold subtest

In contrast to the Sniffin' Sticks threshold test, SMELL-S is self-administered using a computerized app that guides the subjects through the testing paradigm, with subjects entering their responses via the computerized app. The stimulus is composed of a complex odor-mixture, instead of phenylethyl alcohol (rose-like odour) with 10 dilutions in a geometric series. The test starts at a medium difficulty level (level 5 out of 10). The remaining testing procedure is the same as the Sniffin' Sticks threshold test.

6 Conclusion

We presented a novel portable, multi-channel odor delivery device that can deliver a high number of odors flexibly and through personalised digital control. The 24-channel device is significantly more compact and much more affordable compared to existing olfactometer designs. It is self-contained and does not require an external air supply. The use of individual odor channels avoids cross-contamination and the removable odorant cartridges can be easily exchanged between experiments/testing sessions.

The characterisation of the odor delivery device shows that it is possible to deliver multiple odors with high temporal precision to users at short distances, making it ideally suited to research and clinical applications, including for smell testing.

A comparison with a standard Sniffin' Sticks smell test shows that significant time savings can be achieved through automation and the removal human tasks such as capping / uncapping the Sniffin' Sticks. Its digital integration with an app and cloud based ecosystem enables efficient data collection from users, removing the need for laborious manual reporting tasks.

The design provides several unique advantages for investigating smell perception and offers the possibility that users can one day self-administer smell tests in a range of settings, allowing smell healthcare services to evolve and become part of a routine practice of continuous self-monitoring and care for improved health and well-being.

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Declarations

Author contributions. E.M. and M.O. conceived the design concept for the odor delivery device. D.P and R.H. developed the experimental test setup and undertook characterisation tests, with F.U. providing technical guidance. B.N.L. and J.W.H. undertook the clinical trials with the device and analysed the results of the trial data. R.H., D.P. and J.W.H. wrote the paper.

Ethical approval declarations. The smell test study was approved by the institutional ethics review board of Geneva University Hospital and conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects (IRB approval: 2020-02581).

Informed consent. Informed consent was obtained from all participants.

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Appendix A Appendix

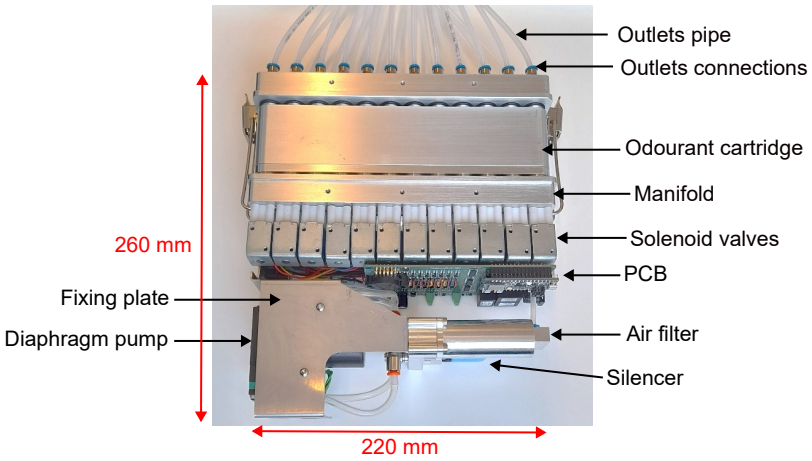

Fig. A1 | Device internals. Image of the internals of the odor delivery device with the case removed showing the main system components.

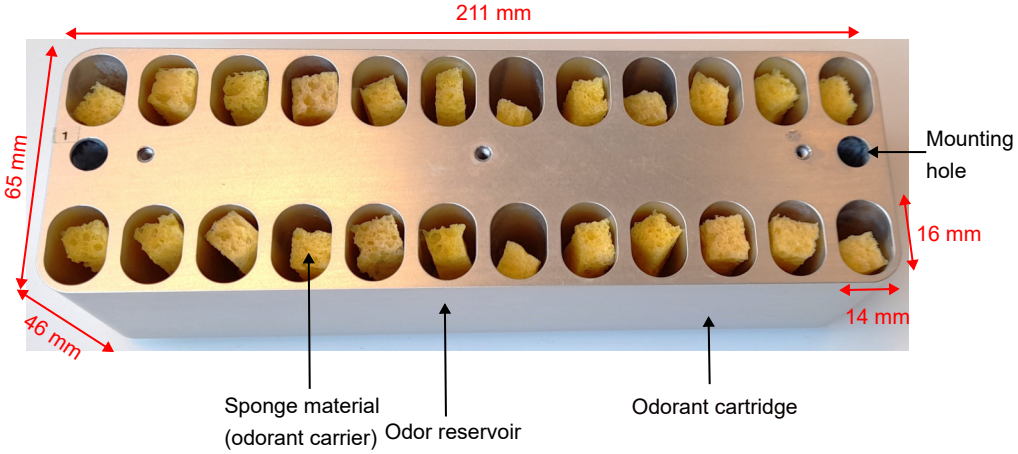

Fig. A2 | Odorant cartridge. Image of the metal odorant cartridge of the odor delivery device showing the 24 odor reservoirs containing the sponge carrier material saturated with the odorant.

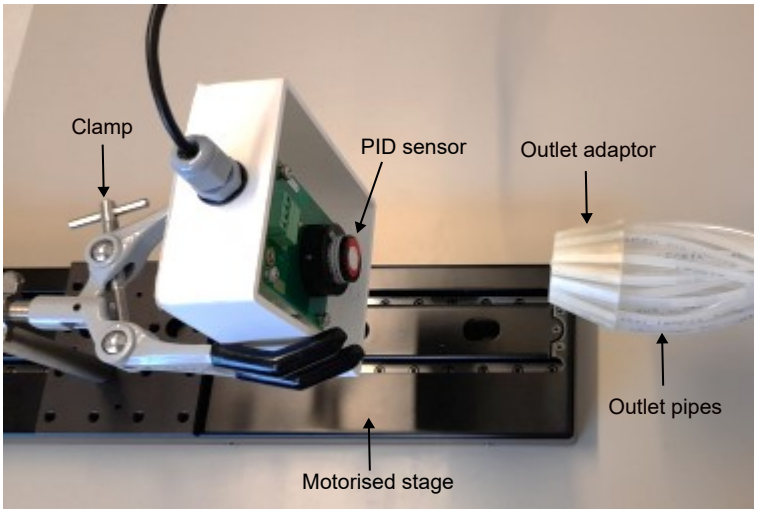

Fig. A3 | Odor mapping test setup. Experimental setup used for mapping the odor distribution. A motorised stage was used to position the PID sensor at different distances from the outlet of the odor delivery device.

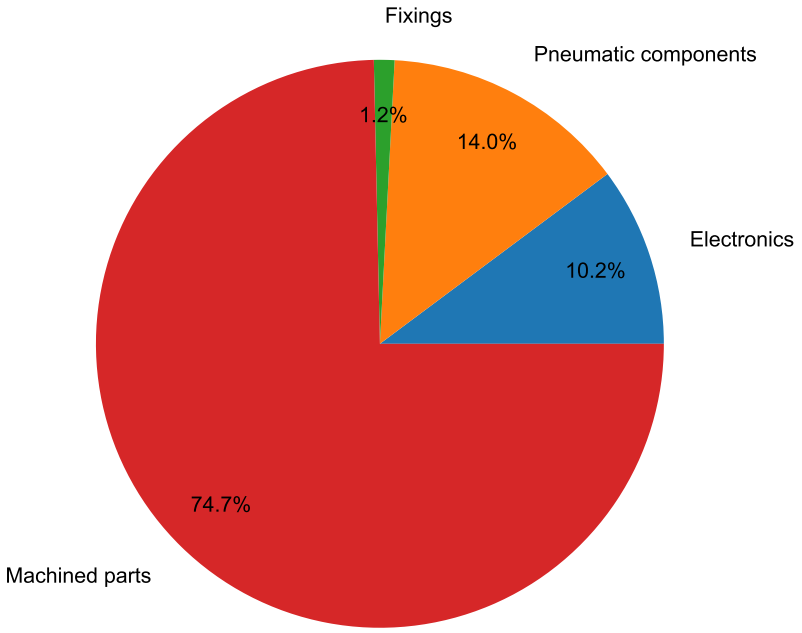

Fig. A4 | Cost breakdown. A pie chart showing the relative cost of the different system components making up the odor delivery device. The cost of the custom machined parts dominates.

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