MASTERARBEIT | MASTER'S THESIS

Titel | Title

Olfactory loss may lead to decreased avoidance reactions and worse health

verfasst von | submitted by

Arnika Margarete Sophie Pehl BSc

angestrebter akademischer Grad | in partial fulfilment of the requirements for the degree of

Magistra pharmaciae (Mag. pharm.)

Wien | Vienna, 2025

Studienkennzahl lt. Studienblatt | Degree programme code as it appears on the student record sheet:	UA 066 605
Studienrichtung lt. Studienblatt | Degree programme as it appears on the student record sheet:	Masterstudium Pharmazie
Betreut von | Supervisor:	Ass.-Prof. Mag. Dr. Iris Stappen

Table of contents

Abstract

Over the last years the sense of smell and its possible pathologies has been viewed with increasing interest. How different diseases can affect the olfactory system leading to parosmia, anosmia and the various other impairments has reached the interest of nearly everyone during the COVID 19 pandemic. In this Master thesis we investigated the approach and avoidance reaction of healthy individuals towards different pleasant and unpleasant odors. The approach and avoidance system is the simplest and most 'ancient' reaction system and is even used by bacteria and such simple lifeforms. We measure this behavior by using a novel approach with a 3D-camera to achieve higher ecological validity. This enabled the participants to stand and move freely within certain limits while the movement was recorded and the odor stimuli rated for perceived pleasantness and intensity. With this approach we found a general reaction to move away from the source of odor, which was differing in strength depending on the pleasantness and intensity perceived by the participant. The more unpleasant the odor, the further the participants moved away from the source, indicating that we found avoidance behavior. The loss of the sense of smell could therefore lead to a loss in avoidance behavior and therefore increase the risk of disease.

Zusammenfassung

In den letzten Jahren entwickelte sich mehr und mehr Interesse an dem Geruchsinn und dessen Pathologien. Die Pandemie, verursacht durch COVID-19, hat verschiedene Krankheiten und wie diese das olfaktorische System beeinflussen und damit zu verschiedenen Beeinträchtigungen, wie u.a. Parosmia oder Anosmia, führen können ins Interesse der Allgemeinheit gerückt. In dieser Master Arbeit untersuchten wir das Annäherungs- und Vermeidungsverhalten von gesunden Individuen gegenüber verschiedenen angenehmen und unangenehmen Gerüchen.
Das Annäherungs- und Vermeidungsverhalten ist das einfachste und älteste Verhaltenssystem, es kann sogar in Bakterien und ähnlich einfachen Lebensformen beobachtet werden. Indem wir dieses Verhalten mit einer 3D Kamera gemessen haben, konnten wir eine höhere ökologische Validität erreichen. Dadurch konnten die Probanden der Studie vergleichsweise frei stehen und mit Limitierungen auch bewegen. Währenddessen wurde die Bewegung durch die Kamera aufgenommen und der Geruch (der Stimulus) wurde freigesetzt und durch den Probanden bewertet.Mit dieser Herangehensweise haben wir einen allgemeinen Trend finden können, der die Reaktion, sich von der Quelle des Geruchs weg zubewegen, zeigt. Dies hängt in Stärke von der wahrgenommenen Annehmlichkeit und Intensität des Geruchs ab.Je unangenehmer der Geruch wahrgenommen wurde, desto weiter entfernten sich die Probanden von der Geruchsquelle, was darauf hindeutet, dass wir ein Vermeidungsverhalten gefunden haben.Der Verlust des Geruchssinns könnte damit zu einem Verlust im Vermeidungsverhalten führen und damit zu einem höheren Risiko für eine Erkrankung.

Acknowledgement

An dieser Stelle möchte ich mich bei Professorin Stappen für ihre Geduld und Unterstützung über die ganze Zeit bedanken. Ich danke auch Johan Lundström und Evelina Thunell für die Führung des Projekts und dass sie mein Erasmus Aufenthalt möglich gemacht haben. Dank auch an Laura, die mir am Anfang alles gezeigt hat. Ich danke Gregorius für die gute Zusammenarbeit und für die Auswertung der Daten. Ich danke Supreet dafür, dass sie mir beim schreiben eine Richtung gegeben hat. Der ganzen Gruppe von Mats und Johan danke ich, dass ich so warm aufgenommen wurde. Und zu guter Letzt meinen größten Dank an Frans, für die Geduld und unablässige Unterstützung im Projekt, beim Schreiben, beim absolvieren der letzten VUs und Prüfungen, wie auch privat mit unserem Sohn. Vielen Dank für die Liebe die ich seit dem Beginn dieser Masterarbeit von Frans und Leo erfahren durfte.

Introduction

The sense of smell, namely, olfaction, is one of the five major sensory modalities in humans. A key function of the olfactory system is disease and toxin detection and avoidance, but it is also used when approaching things with a pleasant smell such as food or flowers. (Croy et al., 2014; Stevenson, 2010) The olfactory loss and dysfunction as health impairment with the possible consequences and compensations are relevant to be understood, especially with a higher number of patients affected after the COVID-19 pandemic. (Stevenson, 2010)

Overview of the olfactory system’s physiology and pathways

The olfactory system is the anatomical and physiological structure needed for smell perception. Genetically the olfactory genes are in regions of chromosomes prone to mutations making the olfactory system highly adaptable which in turn makes the olfactory system better adapted to environmental factors. This leads to a process of little changes in the olfactory receptor structure couple of gene copies by the means of an increased fine scale growth and death of olfactory receptor genes.
Ultimately this results in a diverse olfactory repertoire that differs widely within but especially in between populations, reflecting the cultural and individual preferences. (Sharma et al., 2019)

How an odor molecule enters the olfactory system, becomes an electrical signal, and finally gets processed to a recognition/ response in the human its path will be followed from the beginning.
The specific odor molecule will come from a source of smell. The possible sources have a high variance and can determine the response reaction in the human. For example, it can be body odor, odor from human or animal excretion, food smell, the smell of flowers or trees and many more. From the source the molecule will enter the nose or the mouth while the human is breathing in air. Additionally, it could enter the mouth with the source itself through eating (here the response will be affected by the sense of taste). The former is called orthonasal olfaction and the latter is called retronasal olfaction.

The olfactory system, seen in figure 1, is built up in its lower anatomical part of the nose and the nasal cavities, which are responsible for respiratory passages in the lower parts and for the perception of smell in the upper parts. The odor molecule would enter the nose with air breathed in and then get with the air flow into the upper parts of the nasal cavities. These contain the olfactory mucous membrane. (*Britannica*, 2018.)

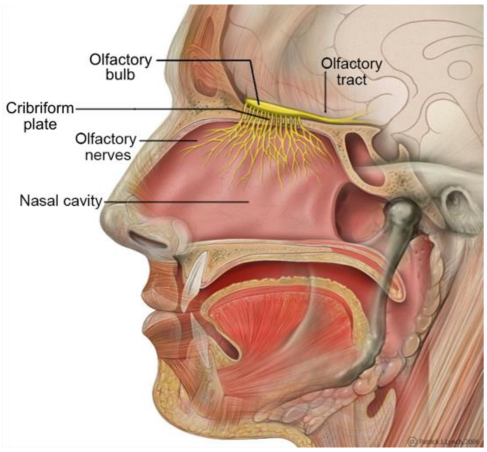

Figure 1) The respiratory and olfactory system until the olfactory tract.

By Patrick J. Lynch, medical illustrator - Patrick J. Lynch, medical CC BY 2.5,

https://commons.wikimedia.org/w/index.php?curid=68379471

In the olfactory mucous membrane, there are around 6-10 million olfactory neurons in humans. Each express one olfactory receptor type on its surface. In the olfactory epithelium are also bowman's glands which secret mucus for lubrication of the mucosa and for dissolving the odor molecules. This ensures that the molecules can be detected by the olfactory neurons. (Doty, 2015)

Each of the olfactory neurons has two projections. One projection is a peripheral dendrite which ends in the form of small radially placed filament on the surface of the olfactory mucous membrane. These filaments are called olfactory hairs and express the olfactory receptor on their surface. The other projection of the olfactory neuron is called olfactory nerve fiber, which is a long and thin, unmyelinated axon. It reaches the olfactory bulb, a part of the forebrain at the base of the frontal lobes. There they meet the dendrites of the second order olfactory neurons, called mitral cell, with a synapse. This means the odor molecules dissolved in the mucus are reaching the olfactory nerves in the olfactory epithelium. There each gets recognized by its corresponding receptor. The resulting signal gets carried directly into the olfactory bulb through an action potential. (Brittanica, 2018) The olfactory bulb has direct connections to the amygdala. This gives olfaction a unique direct connection to the fight and flight centra of the brain. (Doty, 2015). This is in contrast with vision and audition which both are mediated by the thalamus. The mitral cells, the second order olfactory neurons mentioned above, emit many axons, which together form the olfactory tract also seen in figure 1. They end in three different olfactory structures. Most end in the cortex of the piriform lobe (the olfactory cortex), but some end in either the olfactory tubercle or the amygdaloid complex. (Brittanica, 2018) All of this leads to the odor molecule being recognized and the signal processed.

The role of olfaction in disease detection and avoidance.

Given olfaction's unique direct connection to the amygdala it is of no surprise that olfaction is used for disease detection and avoidance across various species. Studies have demonstrated the olfactory abilities of animals like dogs and rats, which have been trained to detect a wide range of infectious and non-infectious diseases through the analysis of body odors, breath, and other biological samples.

For instance, in Clostridium difficile (C. difficile) infection, trained dogs exhibited high sensitivity (92.3%) and specificity (95.4%) in detecting C. difficile in stool samples, and they could locate C. difficile reservoirs in hospital environments (Cambau & Poljak, 2020). In the context of COVID-19, dogs have been trained to detect volatile organic compounds (VOCs) associated with SARS-CoV-2 infection in sweat samples, achieving success rates between 76-100% in distinguishing positive from negative samples (Dickey & Junqueira, 2021). Similarly, African giant pouched rats have been trained to diagnose tuberculosis by smelling sputum samples, with detection success rates comparable to standard microscopy methods (Cambau & Poljak, 2020).

Moreover, olfaction has been instrumental in detecting various cancers, including bladder cancer, melanoma, ovarian cancer, colorectal cancer, and prostate cancer. Dogs trained for cancer detection have demonstrated detection rates exceeding 90% in some studies (Salgirli Demirbaş et al., 2021).

Disease detection and avoidance from actively sick individuals is, however, the most important when you are in contact with such individuals, so that you can avoid being in a contagious environment for a long enough duration to become infected yourself. It is shown that body odors serve as important cues about an individual's health and disease status where certain diseases are associated with distinct body odors, such as a sweet fruity odor in diabetic ketoacidosis or a foul odor in tuberculosis (Shirasu & Touhara, 2011). Experimentally induced sickness can alter body odor within hours, making it more aversive and less healthy-smelling to others (Olsson et al., 2014). The same results was found in naturally acute respiratory infection (Tognetti et al., 2023). Furthermore, individual differences in body odor disgust sensitivity (BODS) are related to how people perceive and respond to body odors, particularly those from strangers, suggesting a link to disease avoidance mechanisms (Olsson et al., 2014).

Impacts of Olfactory loss on Disease and Toxin detection and avoidance.

Olfactory dysfunctions, affecting around 20% of the general population, encompass various types such as anosmia (complete loss of smell), hyposmia (reduced smell), parosmia (altered smell identity), dysosmia (abnormal smell perception), cacosmia (distorted smell recognition), and phantosmia (olfactory hallucinations). These dysfunctions can be categorized based on anatomical and informational processing into peripheral conductive pathologies, often stemming from sinonasal inflammatory diseases or obstructive sinonasal mass lesions, and sensorineural pathologies, typically resulting from disruptions in central olfactory pathways or neural function, caused by factors like viral infections, trauma, congenital conditions or neurodegenerative diseases. (Lie et al., 2021)

The impact of olfactory impairment extends beyond the loss of sensory pleasure. It poses significant challenges in detecting potentially hazardous odors such as fires, gas leaks, spoiled food or disease. The inability to detect these environmental threats through smell presents serious safety risks, leaving individuals vulnerable to infections or remaining in hazardous situations unknowingly. Studies have shown a statistical association between olfactory dysfunction and increased mortality rates, likely attributable to the inability to perceive these dangerous odors. (Schäfer et al., 2021; Van Regemorter et al., 2020) Moreover, the loss of smell can disrupt eating behaviors, as individuals may fail to detect spoiled food, increasing the risk of food poisoning and other related health issues. Thus, olfactory dysfunction not only affects the sensory experience but also jeopardizes safety and overall well-being by impeding the detection and avoidance of environmental toxins and harmful substances. (Schäfer et al., 2021; Van Regemorter et al., 2020)

The approach and avoidance paradigm

Basic approach and avoidance behaviors are generally strongly conserved mechanisms of phylogenetically high age. The neuropsychological systems in humans that are responsible for basic approach avoidance behavior (e.g. out of fear) are very similar to other species and generally seen as primary forms of reactions to motivation and emotion. Approach and avoidance behavior, visualized in figure 2, as in active approach and active avoidance (seen as active withdrawal), can be found in any species starting from as small as a bacterium. These (e.g. bacteria) react for example with active approach towards a gradient of chemicals coming from a source of food and in those for whom light is associated with exposure and danger (which is the case for most species) react with active withdrawal when detecting even simple/small light strengths. In "simpler" species this kind of behavior is not goal oriented, while it becomes goal-oriented in "higher" species. Goals in this context can be positive (leading to active approach) or negative (leading to active avoidance/withdrawal). However, there is not always such an easy distinction in between approach and avoidance for positive and negative goals respectively. Positive motivations can become negative. Common examples for this are consummatory stimuli and economic experiments. If a positive motivated situation/stimuli becomes linked to loss, frustration, or omission it will turn into a negative goal and therefore can then lead to avoidance. The response to this can be associated with the responses by individuals towards pain. This also works vice versa with negative goals becoming positive goals. Therefore, when a positive goal becomes negative or a negative becomes positive, they can be treated the same as negative or positive goals respectively. (Corr & Matthews, 2020; McNaughton et al., 2016)

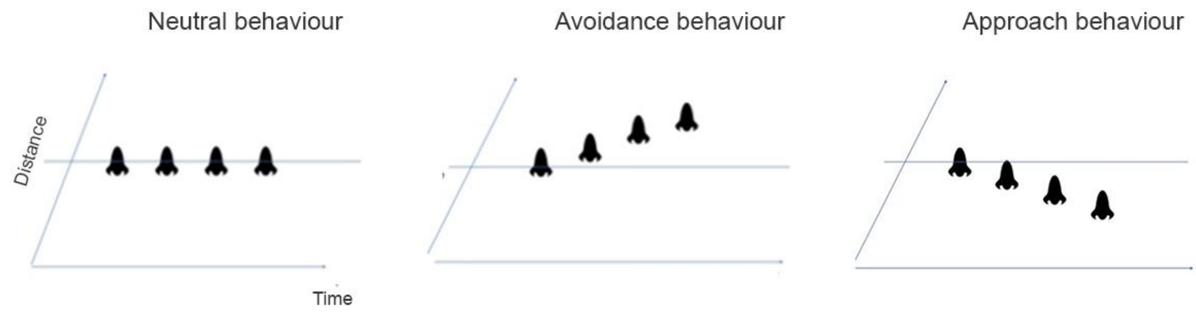

Figure 2: Visualization of approach and avoidance behaviour.

If a second or more goals appear they can be "competing" with each other for the approach and avoidance of an individual depending on different factors. It for example becomes conflicting when the goals are incompatible. The simplest version of this conflict of goals is then called approach-avoidance-conflict. This can lead to passive avoidance or passive approach and dithering around the goal. These behaviors can be shut out with different methods as for example anxiolytic drugs. That does not work with basic, active approach/avoidance. This passive form of approach and avoidance is also phylogenetically old showing anxiolytic benzodiazepine receptors being present from primitive vertebrates on. (McNaughton et al., 2016)

Approach and Avoidance is being researched and used for research in many subfields to psychology and neuroscience. It plays a big role especially in areas like cognitive psychology and neuroscience as well as behavioral neuroscience. [Wikipedia: Psychology, 17.08.23] For example in personality research in psychology it is acknowledged to be of importance in all forms of personality, emotions and motivation. Furthermore, as mentioned above it is of phylogenetic high age and therefore also researched in the subfield of evolutionary neuroscience. (Corr & Matthews, 2020)

To capture the actual behavior, it is of high importance to create a setup with high ecological validity. Previously, approach and avoidance behavior has been captured through arm movements (Phaf et al., 2014) and with higher ecological validity, whole body movements.

A body of evidence suggests that our sense of smell is tightly linked with approach and avoidance behavior, which makes sense given the high age of the olfactory system. One study (Cereghetti et al., 2021) involving whole-body movements has revealed that noxious odors (e.g., skunk odor) slowed the forward locomotion and increased backward inclination, indicative of avoidance tendencies, as opposed to neutral or pleasant olfactory stimuli. Conversely, pleasant odors prompt accelerated forward motion, suggesting an inclination towards approach behavior. Also, a mammalian blood odor constituent, E2D, has been identified as creating an avoidance response in humans (Arshamian et al., 2017). Furthermore, by measuring inclination of the participant, a link between avoidance response to odors and a neural response in motor cortex have been found (Iravani et al., 2021).

Aims and Rationale of current study

Given the importance of a healthy olfactory system in disease detection and avoidance we would like to investigate if we can confirm a link between approach and avoidance behavior and the sense of smell with a higher ecological validity compared to previous studies. Given that we have a population with olfactory loss that has increased in size over the last years it is of importance to investigate whether these individuals will be at higher risks due to not having the same ability to avoid, for example, contaminated food sources or disease. Our research question is hence “Does odor pleasantness induce approach and avoidance behavior in a healthy population?”

The aims of the study is therefore:

1. Setting up an ecologically valid paradigm for testing approach and avoidance behavior based on odor stimulation.
2. Present odors with varying pleasantness and a constant intensity.
3. Test 20 healthy participants for their approach avoidance reaction.

4. Test statistically if the participants approach positive odor stimuli and avoid negative odor stimuli.

Methods

Transparency/Ethics

The ethics of this experiment was approved by the local ethics committee, Etikprövningsnämnden, (2016/1692-31). All participants were informed regarding the study beforehand, and a consent form was signed. In the analysis the participants' identity was kept hidden from the researcher.

Research methodology

In this study we want to control a variable (pleasantness of an odor) to see how that affects approach and avoidance behavior. To investigate this, we will perform an experiment where we operationalize approach and avoidance behavior by deviations in distance from a baseline measure. The uniqueness of this study, compared to previous studies, is that we will show approach and avoidance behaviour in a setting that has higher ecological validity than previous studies. This is achieved by measuring 3D body movements with high precision.

Materials and Methods:

Data collection

To collect the data for the behavioral approach-avoidance experiment video and voice recording was taken of every participant. To capture the approach avoidance behavior a depth camera of the model Intel Realsense D435 was used (Intel technologies, California). This camera can capture images with a depth precision of 2 mm within a range of 1 meter. A script enabled the camera to recognize the tip of the nose of the participant which enabled us to measure the distance from the camera to the participant. For the analysis of this thesis the tip of the nose was used as a single point measure.

EPrime 2 (Psychology Software Tools, Pennsylvania) was used as presentation software and connected to a Lundström Olfactometer (Lundström et al., 2010) and PowerLab 16/35 (ADInstruments, Colorado) through parallel port communication. This setup enabled us to measure the participants breathing and subsequently trigger the odor delivery based on the participants natural breathing cycle. The triggering was done through EPrime at the beginning of the inhalation cycle.

Odors

As stimuli 6 different odors were used. 3 odors mainly perceived as positive, and 3 odors mainly perceived as negative were used. The reason was to make sure every participant would smell and perceive at least two odors as negative and two as positive. The Odors were mixed twice during the testing period to ensure that the experience is similar in between participants.

Table 1) Odors used in the experiment

Odor number	Odor name	Name odorous ingredient	Amount odorous ingredient	Name solvent	Amount solvent
1	Rotten Food	Diethyl Disulfide	7.98 ml	Diethyl Phthalate	0.02ml
2	Urine	Urine odor mix	4 ml	Propanediol	4 ml
3	Parmesan / Vomit	Butyric Acid	0.8 ml	Diethyl Phthalate	7.2 ml
4	Pineapple	Ethyl Butyrate	0.8 ml	Diethyl Phthalate	7.2 ml
5	Grass	Hexenol-3-CIS	0.25 ml	Propanediol	7.98 ml
6	Lilac	Syrén	8 ml	-	-

Olfactometer

A Lundström olfactometer (Lundström et al., 2010) was used to present the odor mixtures to the participants. Through tubes the airflow is connected to glass jars containing the different odor mixtures and a tube in front of the participant presenting the odor. This leads to “the air flowing” through the tubes, taking up / saturating with the odors in the glass jars and then flowing through more tubes to the one where it exits the system and is presented to the participant. To ensure stability, the strengths of the airflow were tested with an Gilian Gilibrator 2 (Sensidyne, Florida) and if needed adapted in the beginning of every testing day. Every odor is separately stored in a glass jar. Through valves that are controlled by digital signal from EPrime it is controlled which odor gets presented to the participant.

Participants

The Recruitment was done through the KI recruitment system SONA with several requirements in place. The requirements were as following: Normal or corrected to normal vision (glasses or contact lenses), age between 18 and 45 years, the participant should not suffer from dizziness, vertigo, or balance problems, should be able to stand for 10 minutes, should not have neurodegenerative disorders, nor ADHD diagnosis, should have a normal sense of smell, no congested nose and above 160 cm of body height.

Many participants, that participated with the “new” system in the beginning, were smaller. Furthermore, the participants were not supposed to eat or drink anything except water for half an hour directly before the experiment.

All participants received 200 SEK as reimbursement (as transfer to their bank accounts or in form of gift vouchers). In total 25 participants were tested.

Odor threshold identification test

To be eligible to participate in the study the participant needs to have an ability to smell. Therefore, we implemented an odor identification threshold test. 5 Sniffin’ Sticks out of the Burghart Sniffin’ Sticks Identification Test 16 (blue version) (Hummel et al., 1997) were used to evaluate if the olfactory performance of the participants was below threshold before performing the study. The threshold was set at identifying 3 out of 5 presented odors correctly. Everyday odors (Cinnamon, Banana, Grapefruit, Licorice, Garlic) were chosen out of the 16 odors containing test kit. The participant had to choose the correct answer out of 4 possibilities given per odor. Important is that every Sniffin’ Stick is presented to the participant by the testing person and that the participant does not hold the stick in their own hand. This prevents the possibility of contamination of the participants hands with the odors of the Sniffin' sticks and makes the presentation of the stick more comparable in between the participants.

Experimental Design / Procedure

The study was performed with one session of approximately 90 minutes per participant. The session consisted of 4 blocks with odor presentation, 15 trials per block. In each trial the participant was first presented with a fixation cross with a variable timing between 1-2 seconds. After the fixation cross the sampling of the inhalation phase starts and when the inhalation phase was detected the odor was presented for 1 second. The order of the odors throughout the experiment was randomized but balanced in between each block. After each odor presentation the participant was asked to rate the odor on a scale from 1-9 regarding pleasantness (1=very unpleasant, 9= very pleasant) and intensity (1=not perceived, 9=very intense). The participant sayed this out loud and it was transferred to an electronic table by the experimenter.
The participant was wearing a nasal cannula to measure breathing, earplugs and headphones. Headphones and earplugs were used to block their hearing to avoid auditory cues from the olfactometer when the odors are getting released, so that it is clear they were reacting to the actual odor and not to the sound of the release.

To ensure that the odor would be released in the beginning of the inhale a threshold according to every individual's breathing data was set and adjusted to consider each individuals breathing pattern. To make sure the threshold is set correctly from the first trigger on participants were asked to wear the cannula and breath normally and calm but only through their nose for approximately 2 minutes before the first block of the study. In that time the threshold was set manually by the experimenter. It is necessary for the participant to breathe only through the nose, because the cannula, with which the breathing is measured, is only applied to the nose. This 2-minute step was done in the experimental room and with a closed door to ensure minimum distraction.

The participant was asked to always stand with their feet behind a line marked out on the floor. The outlet of the olfactometer was then put at a distance of 60 cm from the participant's nose. This is to enable high precision from the 3D-camera and enable ecological validity regarding odor presentation.

Data analysis

To determine whether any significant effects on pleasantness perception on approach and avoidance behavior could be seen we decided to apply a linear model. To consider effects due to odor intensity a model with two predictor variables, i.e. rated pleasantness and rated intensity, was created. In this model all the data from all participants was investigated. The linear model was implemented in Matlab version 2022b.

Results

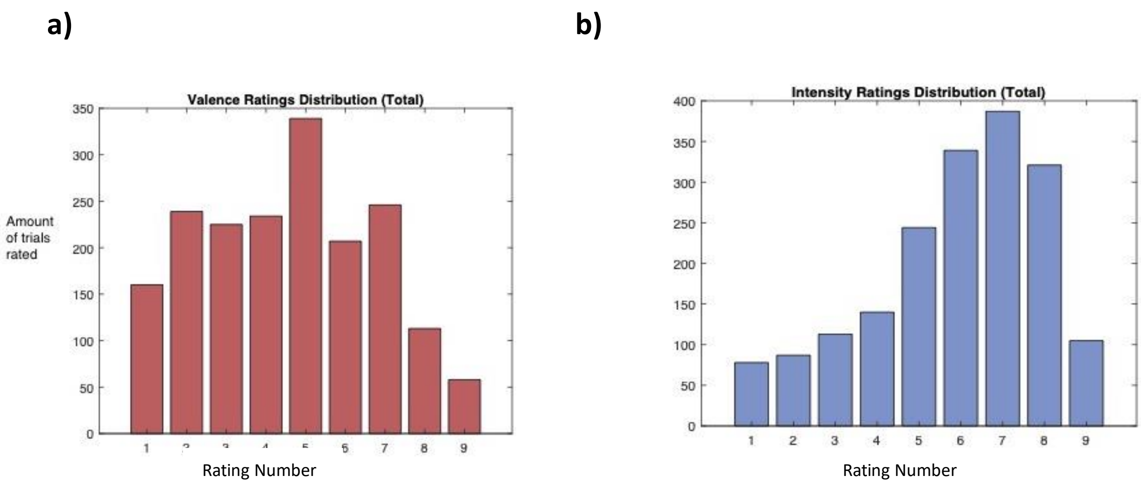

Figure 3) Rated valence and intensity for the trials in the experiment where 1-9 are the possible ratings. a) Rated valence where 1 shows the least pleasant rating for an odor and 9 shows the most pleasant rating. **b)** Rated intensity for all trials where 1 shows the least intense rating for an odor

In our experiment we were able to capture the whole range of valence from very unpleasant to very pleasant, as can be seen in figure 3a. While most trials are rated with a neutral 5, we see that the distribution of ratings contains all ratings with a somewhat stronger tendency towards unpleasant (1-4). This is in contrast to the rated intensity, seen in figure 3b where we see that the odors were rated more even with regards to intensity.

a) **b)**

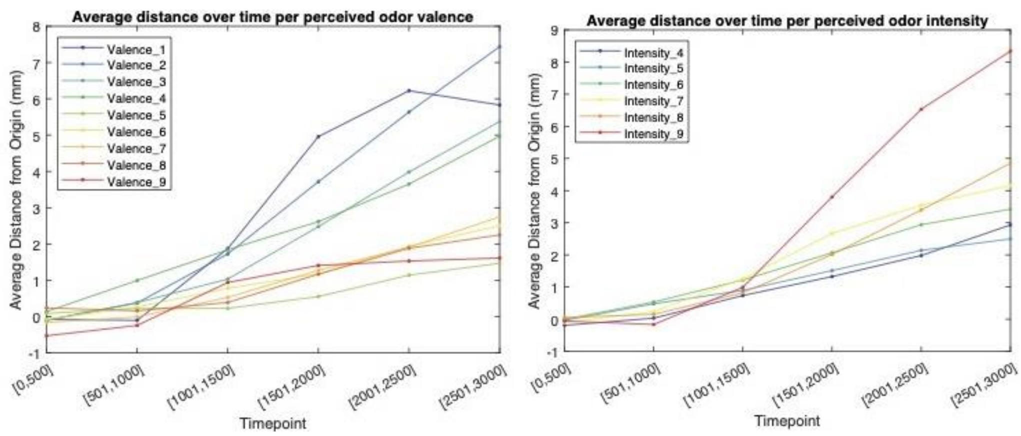

Figure 4: Distance moved from center based on a) Rated Pleasantness (valence). **b)** Rated intensity.

Mainly avoidance responses were seen for both odor valence and odor intensity as can be seen in figure 4. Here we can follow the timecourse after odor delivery where the differently colored lines represent the different ratings of the stimuli. What we see here is that all rated stimuli induce a response to move backwards from the odor source. However, stimuli that is rated more intense or unpleasant induces stronger backwards movement.

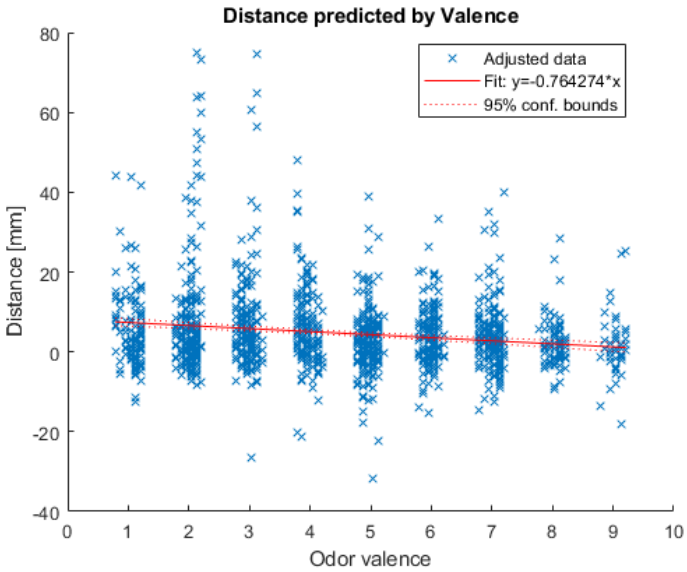

Figure 5) Linear regression of how well odor pleasantness rating predicts a change in distance in mm from the source location. A clear linear trend regarding avoidance for more unpleasant trials are seen. p<2.8e-11.

To see whether the backwards movement where significantly dependent on odor valence we created a linear model with the distance from the source at time point 2000 ms as the predicted variable and rated odor valence and intensity as the predictor variables. Here we found that distance from the source is significantly dependent on rated odor valence with p < 2.8-e11, as can be seen in figure 5. Table 2 shows the results from the linear model where we see that both odor pleasantness and odor intensity effects approach and avoidance behavior.

Table 2) Parameter values of the linear model containing rated valence and intensity as predictor variables and distance from the odor source as predicted variable. Clear significant difference regarding the effect of

Variable	Estimate	Standard error	t-test	p-value
Pleasantness	-0.76	0.11	-6.7	2e-11
Intensity	0.81	0.18	4.5	9e-6

Discussion

In a healthy population, the interaction between olfactory perception and motor response plays an important role in guiding behavior, particularly in the context of approach and avoidance behavior towards olfactory stimuli. Research consistently demonstrates that pleasant odors elicit approach behaviors, whereas unpleasant or aversive odors prompt avoidance responses (Cereghetti et al., 2021; Iravani et al., 2021). This approach and avoidance effect shows the adaptive nature of the olfactory system in facilitating appropriate behavioral responses to environmental cues.

In our study we showed that this kind of approach and avoidance behavior exists in a healthy population in an ecologically valid environment. Our results show a trend where the participants always move away from the source of odor. However, there is a clear difference in how much they move away based on the pleasantness of the odor. This is further supported by our regression analysis where we see a clear relation between rated odor pleasantness and distance moved away from the point of origin. This is in contrast to other studies that show both approach and avoidance (Iravani et al., 2021) or that the participants only show approach behavior (Cereghetti et al., 2021).
One theory we have is that the participants are eager to perform and, since we told them specifically where the odor comes from, they are moving towards it artificially awaiting the odor. Therefore, there could be a slight movement away just as a response to the awaited odor arriving. This is not optimal and should be addressed as a problem to change in possible future studies.

It is interesting to note that the neutral rated odor stimulus shows the lowest amount of distance moved away from the source. This could potentially be explained by the effect on odor intensity on the postural behavior. We do show here that odor intensity influences how much the participants lean back, where the strongest intensity is the one showing the biggest distance created towards the source of the odor. In our regression model we included intensity as a covariate and saw that there is an effect from the intensity of the odor stimuli on the distance moved away from the origin as well. That our stimulus was more intense compared to previous studies could hence explain the difference between our results and previous studies.

Our ability to accurately perceive and appropriately respond to olfactory stimuli is important for navigating social interactions, ensuring food safety, and avoiding potentially hazardous situations. Healthy individuals are good at discriminating between different odors and quickly adjust their behavior based on the perceived pleasantness or aversiveness of the olfactory cues. However, in populations with olfactory dysfunction, such as anosmia or hyposmia, the relationship between olfaction and motor behavior may be disrupted. Individuals with olfactory dysfunction may exhibit altered approach-avoidance behaviors towards olfactory stimuli due to their impaired ability to perceive and interpret odor cues accurately.

Individuals with olfactory dysfunction may have difficulty discriminating between pleasant and unpleasant odors, leading to decreased approach-avoidance responses. For example, individuals with anosmia may not have the typical avoidance response towards noxious odors, potentially increasing their risk of exposure to harmful substances or disease. Conversely, they may also fail to exhibit approach behaviors towards pleasant odors, which could impact their overall quality of life and social interactions (Winter et al., 2023).

Such patient groups would hence have an elevated risk of needing secondary pharmaceutical treatment which could show up in a need for fever decreasing products if infected from a diseased individual, or antidepressants when their quality of life goes down due to a lowered hedonic appreciation of their environment. Additionally, a lower safety of foods, missing e.g. that the milk is sour, can lead to different diseases or problems for the individual. To create such interventions would not be necessary if the main problem, their olfactory dysfunction, would be improved.

While studies show that olfactory training both can improve the sense of smell in individuals it also puts a lot of pressure on the patient to perform the smell training (Winter et al., 2023). This is usually associated with problems of adherence (Haas et al., 2024).

A limitation of this study is that we only ended up using one of the points collected with the 3D camera. This was mainly done to make the analysis easier. The point chosen is, however, the point that would give the best representation of both small and big head movements away and to the source. This still gives the study a high ecological validity.

One thing that was noted while performing the experiment was that participants tended to rate odors that they did not perceive as neutral in pleasantness. How this affects our results is unclear and is something that needs to be investigated in a further analysis.

There was also the problem of one of the odors being unstable and changing smell during the beginning, which later was avoided by preparing the odors more often.

Conclusions and future work

From our results we can conclude that odor pleasantness is inducing approach and avoidance behavior and that it is mediated by odor intensity. We can also conclude that the population of individuals with olfactory loss is a population that needs new ways of treating their condition, else they are at risk of other diseases and hence in need of unnecessary use of pharmaceuticals. To develop more effective smell training methods should hence be prioritized in future works.

References

Arshamian, A., Laska, M., Gordon, A. R., Norberg, M., Lahger, C., Porada, D. K., Jelvez Serra, N., Johansson, E., Schaefer, M., Amundin, M., Melin, H., Olsson, A., Olsson, M. J., Stensmyr, M., & Lundström, J. N. (2017). A mammalian blood odor component serves as an approach-avoidance cue across phylum border - from flies to humans. *Scientific Reports*, *7*(1), 13635. https://doi.org/10.1038/s41598-017-13361-9

Cambau, E., & Poljak, M. (2020). Sniffing animals as a diagnostic tool in infectious diseases. *Clinical Microbiology and Infection*, *26*(4), 431–435. https://doi.org/10.1016/j.cmi.2019.10.036

Cereghetti, D., Faye, P., Gros, L., Mahé, L., Diaz, E., Cayeux, I., Heritier, T., & Versace, R. (2021). Validation of New Methods of Using Simulated Whole-Body Movements as Implicit Indicators of Sound and Odor Preferences. *Frontiers in Psychology*, *12*, 659269. https://doi.org/10.3389/fpsyg.2021.659269

Corr, P. J., & Matthews, G. (Eds.). (2020). *The cambridge handbook of personality psychology*. Cambridge University Press. https://doi.org/10.1017/9781108264822

Croy, I., Nordin, S., & Hummel, T. (2014). Olfactory disorders and quality of life--an updated review. *Chemical Senses*, *39*(3), 185–194. https://doi.org/10.1093/chemse/bjt072

Dickey, T., & Junqueira, H. (2021). Toward the use of medical scent detection dogs for COVID-19 screening. *Journal of Osteopathic Medicine*, *121*(2), 141–148. https://doi.org/10.1515/jom-2020-0222

Doty, R. L. (Ed.). (2015). *Handbook of olfaction and gustation*. John Wiley & Sons, Inc. https://doi.org/10.1002/9781118971758 (pages 37-62)

Haas, M., Raninger, J., Kaiser, J., Mueller, C. A., & Liu, D. T. (2024). Treatment adherence to olfactory training: a real-world observational study. *Rhinology*, *62*(1), 35–45. https://doi.org/10.4193/Rhin23.207

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). "Sniffin" sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses*, *22*(1), 39–52. https://doi.org/10.1093/chemse/22.1.39

Iravani, B., Schaefer, M., Wilson, D. A., Arshamian, A., & Lundström, J. N. (2021). The human olfactory bulb processes odor valence representation and cues motor avoidance behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(42). https://doi.org/10.1073/pnas.2101209118

Lie, G., Wilson, A., Campion, T., & Adams, A. (2021). What's that smell? A pictorial review of the olfactory pathways and imaging assessment of the myriad pathologies that can affect them. *Insights into Imaging*, *12*(1), 7. https://doi.org/10.1186/s13244-020-00951-x

Lundström, J. N., Gordon, A. R., Alden, E. C., Boesveldt, S., & Albrecht, J. (2010). Methods for building an inexpensive computer-controlled olfactometer for temporally-precise experiments. *International Journal of Psychophysiology*, *78*(2), 179–189. https://doi.org/10.1016/j.ijpsycho.2010.07.007

McNaughton, N., DeYoung, C. G., & Corr, P. J. (2016). Approach/Avoidance. In *Neuroimaging personality, social cognition, and character* (pp. 25–49). Elsevier. https://doi.org/10.1016/B978-0-12-800935-2.00002-6

Brittanica, Olfactory system | Parts, Function, & Organs. (2018). Retrieved October 10, 2024, from https://www.britannica.com/science/olfactory-system

Olsson, M. J., Lundström, J. N., Kimball, B. A., Gordon, A. R., Karshikoff, B., Hosseini, N., Sorjonen, K., Olgart Höglund, C., Solares, C., Soop, A., Axelsson, J., & Lekander, M. (2014).

The scent of disease: human body odor contains an early chemosensory cue of sickness. *Psychological Science*, *25*(3), 817–823. https://doi.org/10.1177/0956797613515681

Phaf, R. H., Mohr, S. E., Rotteveel, M., & Wicherts, J. M. (2014). Approach, avoidance, and affect: a meta-analysis of approach-avoidance tendencies in manual reaction time tasks. *Frontiers in Psychology*, *5*, 378. https://doi.org/10.3389/fpsyg.2014.00378

Salgirli Demirbaş, Y., Sareyyüpoğlu, B., Öztürk, H., Kismali, G., Alpay, M., Seçilmiş Canbay, H., Emen, F., Baş, B., & Özkul, A. (2021). The role of bio-detection dogs in prevention and diagnosis of infectious disease: A systematic review. *Ankara Üniversitesi Veteriner Fakültesi Dergisi*. https://doi.org/10.33988/auvfd.834133

Schäfer, L., Schriever, V. A., & Croy, I. (2021). Human olfactory dysfunction: causes and consequences. *Cell and Tissue Research*, *383*(1), 569–579. https://doi.org/10.1007/s00441-020-03381-9

Sharma, A., Kumar, R., Aier, I., Semwal, R., Tyagi, P., & Varadwaj, P. (2019). Sense of smell: structural, functional, mechanistic advancements and challenges in human olfactory research. *Current Neuropharmacology*, *17*(9), 891–911. https://doi.org/10.2174/1570159X17666181206095626

Shirasu, M., & Touhara, K. (2011). The scent of disease: volatile organic compounds of the human body related to disease and disorder. *Journal of Biochemistry*, *150*(3), 257–266. https://doi.org/10.1093/jb/mvr090

Stevenson, R. J. (2010). An initial evaluation of the functions of human olfaction. *Chemical Senses*, *35*(1), 3–20. https://doi.org/10.1093/chemse/bjp083

Tognetti, A., Williams, M. N., Lybert, N., Lekander, M., Axelsson, J., & Olsson, M. J. (2023). Humans can detect axillary odor cues of an acute respiratory infection in others. *Evolution, Medicine, and Public Health*, *11*(1), 219–228. https://doi.org/10.1093/emph/eoad016

Van Regemorter, V., Hummel, T., Rosenzweig, F., Mouraux, A., Rombaux, P., & Huart, C. (2020). Mechanisms linking olfactory impairment and risk of mortality. *Frontiers in Neuroscience*, *14*, 140. https://doi.org/10.3389/fnins.2020.00140

Winter, A. L., Henecke, S., Lundström, J. N., & Thunell, E. (2023). Impairment of quality of life due to COVID-19-induced long-term olfactory dysfunction. *Frontiers in Psychology*, *14*, 1165911. https://doi.org/10.3389/fpsyg.2023.1165911