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The influence of diseases on human body odor and its effect on behavior of others

Bakalárska Práca

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PREHLÁSENIE

Prehlasujem, že som bakalársku prácu vypracoval samostatne. Všetky použité pramene a literatúra boli riadne citované. Zároveň súhlasím s eventuálnym zverejnením práce v tlačenej alebo elektronickej podobe. Práca nebola použitá k získaniu iného alebo rovnakého titulu.

V Prahe dna 26.07.2021

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POĎAKOVANIE

Na tomto mieste by som sa veľmi rád poďakoval svojej vedúcej práce Mgr. Jitke Třebickej Fialovej, Ph.D., bez ktorej pomoci by práca nemohla vzniknúť. Vážim si jej čas, rady, ochotu, spätnú väzbu, trpezlivosť, odporúčania, ale aj zmysel pre humor.

Najmä vďaka nej sa mi podarilo prácu napísať aj v tomto náročnom období pandémie.

ABSTRAKT

Napriek tomu, že čuch je jeden z najviac podceňovaných ľudských zmyslov, telesná vôňa je veľmi dôležitá a neoddeliteľná súčasť života každého človeka. Ovplyvňuje ju množstvo rôznych faktorov vrátane vplyvov prostredia, aj génov. Patrí tam aj zdravotný stav človeka a ukazuje sa, že niektoré genetické, infekčné, ale aj neurologické, či psychiatrické poruchy ovplyvňujú jej intenzitu a kvalitu. Majú však vplyv na správanie ostatných? Práca má za cieľ prostredníctvom literárnej rešerše preskúmať akým spôsobom rôzne choroby menia telesnú vôňu, akú hrajú rolu čuchové vodítka súvisiace s chorobami v behaviorálnom imunitnom systéme, priblíži ich vplyv na spoločnosť a medziľudské interakcie a zároveň uvedie využitie v medicínskej diagnostike.

Kľúčové slová: telesná vôňa, prchavé organické zlúčeniny, správanie, behaviorálny imunitný systém, diagnostika

ABSTRACT

Even though olfaction is one of the most underrated from human senses, human body odor is a vital and inseparable part of every individual's life. It is influenced by a variety of genetic and environmental factors. One of those is health status, as it turns out that some genetic, infectious, neurological and psychiatric diseases and disorders impact quality and intensity of human body odors. Do they have any influence on the behavior of others? The aim of the bachelor thesis is to review relevant literature and examine in what way do diseases and disorders change body odor, what role do disease-related olfactory cues play in behavioral immune system, to see their effect on society and interindividual relations and at the same time introduce the potential of disease related odors in diagnostics.

Key words: body odor, volatile organic compounds, behavior, behavioral immune system, diagnostics

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Introduction

Apparently, 53% of young adults would rather give up their sense of smell rather than one of their technological devices (McCann Worldgroup, 2011). Perhaps not as shocking in a world where olfaction is rather underrated and often mocked as not as important compared to vision, or hearing (Majid et al., 2018). However, olfaction is essential in providing us with necessary details about others and the environment. It helps people to enjoy food, protect themselves from environmental hazards and has a role in social interactions.

People also emanate odors that are complex unique prints of every individual that convey important information about one's age, sex, reproductive status, diet, emotional state, and even health status. Some infectious, genetic, and even psychiatric diseases may have an impact on how one smells and could possibly alter consequent interactions and the behavior of others towards the individual.

Pathogens have always been a threat for living organisms including humans and served as selective pressure throughout evolution. Hence, it was beneficial to avoid them and save the body's energy required for their combat. It appears that olfactory cues could play a role in pathogen detection in the environment and help the individual not to get infected.

This theoretical thesis paper will critically review and evaluate current scientific research within the field of human body odors, illnesses/diseases, behavioral immune system and diagnostics. As stated above, health status has been linked to the quality of human body odor. Therefore, this thesis seeks to investigate if and how do illnesses/diseases alter human body odor. Consequently, it aims to research how do the disease-related human body odors influence the behavior of others through the lens of behavioral immune system. In addition, it aims to cover how can olfactory cues be helpful in the field of diagnostics and what is the potential in the analysis of them.

Furthermore, possible prospects and future directions within the topic of human body odors and behavior will be discussed, as well as the limitations of the current studies.

The main goal of the thesis is to answer the following research questions:

.Do various illnesses/diseases influence human body odor?

.Do human body odors related to illnesses/diseases affect human behavior? How?

.Do human body odors play a role in behavioral immune system?

.Can human body odors be used in diagnostics of various illnesses/diseases?

Methods

To answer the main set of thesis questions, systematic literature search will be performed. The objective is to systematically search for keywords “body odor AND illnesses”, “body odor AND sickness”, “body odor AND diseases”, “body odor AND behavioral immune system”, “body odor AND behavior”, “body odor AND disgust”, “body odor AND avoidance” and its synonyms, predominantly focusing on the studies of humans, in the following scientific databases: Web of Science, ScienceDirect, PubMed, the Royal Society. Other topic-relevant studies are to be found by cross-referencing, or by a visual tool Connected Papers. In the selection process of research papers containing relevant information for the thesis - firstly the title, then the abstract and finally the text will be read and evaluated. As most research within the topic is conducted internationally, mainly English studies will be reviewed. Thereafter, the studies will be contrasted and used to answer the main questions of the thesis.

1.The Origins of Human Body Odor

It has been well established that all individuals constantly emanate odorous and non-odorous volatile organic compounds (VOCs) which might be perceived by others. Each person has a specific body odor signature, a unique body odor print that is analogous to a fingerprint distinguishing all individuals apart. It is a result of a combination of various odorous VOCs emitted from different parts of the body (Shirasu & Touhara, 2011). Even though, the categorization of human body odor sources often differs throughout literature, it usually includes skin, the oral cavity, the scalp and hair, palms, soles, anogenital region and axillae as key sources (Ellis, 1927). Nonetheless, urine, feces, vomit, vaginal secretions, or blood as well emit numerous VOCs that make up the original human body odor. Moreover, VOCs could be analyzed, especially regarding the smell of diseases. However, skin odor – particularly the odor emitted from the axillae – is characterized as most distinctive in adults and has been researched most.

Some of the reasons of the focus is the fact that adults' axillae are one the most odorous body regions due to high concentration of apocrine sweat glands, or the convenience of collecting samples. In addition, it is a closed protected place with high humidity which serves as a convenient habitat for various bacteria. More specifically, mainly lipophilic *Corynebacteria* dominant in the region is responsible for the production of malodorous VOCs that is perceived as "sweaty" (Taylor et al., 2003). Moreover, it is assumed that humans adopting bipedalism means that interpersonal communication transferred from anogenital region to axilla due to its convenient location (Han, 2015). Occasionally, the odors of palms, feet or back are collected, but the studies are scarce. In some studies which cover mother-infant chemical communication, the odors of breasts and areolas that are rich in sebaceous glands and Montgomery glands are used to study attachment, or the initiation of breast-feeding (Doucet et al., 2009; Vaglio, 2009).

Mostly, in research covering the odors of diseases and illnesses, axillary odor is used for the reasons stated above. However, as sicknesses often impact the odor of urine and breath, some studies work and analyze those sources. Hence, for the purposes of this work, the mechanisms of body odor formation in axillary area, breath and urine odor will be discussed further, as they are the most frequently used and analyzed odor sources in relation to diseases.

1.1 Skin Glands

Predominantly, skin is the main area contributing to the overall human body odor signature, as it is covered with eccrine, apocrine, and sebaceous glands that produce secretions which interact with skin bacteria, from which VOCs derive. The glands produce odorless secretions, the resulting body odor is created by the metabolic processes of skin bacteria (Shelley et al., 1953). All glands are differently scattered across the body – consequently each region has a specific VOC profile and a different odor (Gallagher et al., 2008; Lowe & Anderson, 2015).

Sebaceous glands are distributed all over the entire body, except for the soles and palms. Most sebaceous glands cover the skin of the head, forehead, cheeks, and chin. They are predominantly found near apocrine glands and associated with hair follicles and as the hair grows, the glands cover it with sebum. The functions of the sebaceous glands are affected by steroid hormones, mostly by androgens, estrogens, progesterone, glucocorticoids, or thyroid hormones (Thody & Shuster, 1989). They produce odorless sebum, an oily secretion consisting primarily of lipids that lubricate and protect the skin and hair, for example from UV radiation (Folk & Semken, 1991). Moreover, sebaceous glands help to regulate body temperature. The excreted sebum mixed with sweat slows down the rate of evaporation in warm conditions, whilst in cool conditions it helps with preventing heat loss (Baker, 2019).

Apocrine glands are located deep in the dermis of the skin and its ducts open to the hair follicles associated with sebaceous glands and distinct secretion. They are concentrated in multiple body areas, mostly those where hair grow, including areolae and genital regions, but can be present on the eyelids and in the skin of the external auditory canal as well. However, the highest concentration of apocrine glands is in the axillary region where they are most prominent in size and activity (Schaal & Porter, 1991). They produce lipids, steroids, and proteins with milky and viscous consistency. These secretions contain carboxylic acids and inorganic substances which are transformed into volatile odorous substances by bacterial enzymes (Natsch et al., 2006). Generally, apocrine glands become fully active in puberty, as their development is based on sex hormones; but in women their activity decreases in menopause, and they become non-functional. Even sex differences have been identified in their size and amount. In males they tend to be larger, whilst females sometimes have a larger amount of them (Doty, 1981).

Eccrine glands represent sweat glands that cover the entire body independent of hair follicles but are most numerous on the palms of the hands, soles of the feet, forehead, in the axilla, on the chest, and between the hair on the scalp (Lowe & Anderson, 2015). In contrast to a more viscous apocrine sweat, eccrine sweat glands secrete clear, odorless aqueous solution consisting of water, small traces of salts, proteins, amino acids, urea, ammonia, and lactic acid (Schaal & Porter, 1991). They lie in the outer region of the dermis and are smaller than apocrine glands, for that reason they are also known as small sweat glands. While some are activated by thermal stimuli, others are activated by psychological stimuli such as emotional state including stress, anxiety, anger, and their production increases under the influence of sympathetic nervous system (Martin et al., 2011). Their key function is thermoregulatory (Lowe & Anderson, 2015).

In addition to apocrine and eccrine glands, apoeccrine glands were discovered that share properties of both types. Apoeccrine glands have an apocrine-like opening of its secretory tubule, but similarly to eccrine glands they have long thin ducts opening directly into the skin, not into a hair follicle. According to data, apoeccrine glands develop during puberty from eccrine and eccrine-like sweat glands in the axillae and anogenital region (van der Putte, 1991). Remarkably, they are present in adult humans' axillary region regardless of their sex, or ethnicity. They produce higher quantities of sweat which suggests their contribution to overall axillary moisture (Sato et al., 1987). Currently, further research is necessary to accumulate more knowledge about the glands, as they are often omitted in general discourse.

1.2 Skin Microflora

As mentioned above, fresh substances produced by sebaceous, apocrine, and eccrine glands lack odorous properties. Those are the result of metabolic action by a range of microbiota residing in and on the epidermis. The skin flora of healthy adults contains bacteria and yeasts. They metabolize the mixture of excretions of the glands and produce various VOCs (Gower & Ruparelia, 1993). Each body region composes of a specific ratio of microorganisms which result in different properties of the emanated odors (Schaal & Porter, 1991). It has been shown that bacteria of the genera *Staphylococcus, Micrococcus, Corynebacterium, Propionibacterium*, *Firmicutes* and *Actinobacteria,* and the yeasts of the genus *Malassezia* are contained in the resident microflora (Costello et al., 2009; Leyden et al., 1981). Micro-floral composition is quite individual and unique. However, some general within sex commonalities could be observed. The body odor of males is often rated as musky, while female odor as sweet. Males tend to have a more intensive and stronger odor compared to females, as they usually have more coryneform-dominated flora. On the other hand, females usually have higher concentrations of coccal-dominated flora (Jackman & Noble, 2006). Importantly, various microflora residents are associated with different types of quality and rating of the odors. Axillary malodor was associated with corynebacterial as the primary agent in the study by Taylor et al. (2003). The same study found no association of malodor and the presence of *Staphylococci*, *Propionibacterium* or *Malassezia* fungi.

Although not all the main constituents that contribute to the resulting skin body odor have been fully discovered and understood, based on chemical assays it appears that fatty carboxylic acids with short and medium carbon chains C2-C10 are important in forming human body odor (Zeng et al., 1991). Another class contributing to the perception of axillary sweat odors are sulfanylalkanols characterized by a pungent odor. They are present in small qualities, but they contribute to the resulting odor, as they have a high volatility and a low threshold (Natsch et al., 2004). For long, it was thought that 16-androstene steroids (androstadienol, androstadienone, androstenone, and androstenol) often described having a musty urine like quality of smell (although different classes have different quality) could make up the resulting body odor. However, they are no longer considered as having the main role in contributing to the odor, as previously believed (Austin & Ellis, 2003).

1.3 Breath Odor

Despite the above-mentioned fact, human body odor can be derived from other regions as well, for example, from the oral cavity. Breath odor is important in human interactions offering cues of one’s diet, or even some illnesses like the sweet-smelling breath of diabetes. The breath of healthy individuals contains a mixture of oxygen, nitrogen CO_2, H_2O, inert gases, and a small fraction of diverse trace quantities (Pandey & Kim, 2011). The volatiles originate in respiratory system, digestive system, and by processes of bacteria in the mouth. By now, more than thousand VOCs have been identified in human breath. However, it has been researched that VOCs in breath differ quantitatively and qualitatively in humans and the external environment has an impact on the breath sample too.

In other words, VOCs detected in the human breath could be endogenous (generated in the body), or exogenous (contaminated by environmental pollutants) (Ligor et al., 2008). Despite the fact, some VOCs have been interdependently recognized in all humans. The distinct VOCs detected in the human breath contain isoprene, ethane, ethanol, pentane, methanol or acetone, and other alcohols. In volume, their concentration ranges from parts per trillion to parts per million. However, their amounts might fluctuate based on diverse factors like use of tobacco products, drugs, specific diet, or exercise routine. For example, smoking increased exhaled ethane and pentane levels, exercising decreased isoprene concentrations (Miekisch et al., 2004). Breath odor can be used in clinical practice as well. Recognition of VOCs in human breath and their thorough analysis can be useful in the field of clinical diagnostics, as potentially disease-related VOCs could be distinguished from the others (Pandey & Kim, 2011).

1.4 Urine Odor

Human urine is one of the body odors sources that is not normally part of human social interactions, however, as it mirrors the internal metabolic and physiological state of the organism, often changes its odor quality with a disease/illness (Schaal & Porter, 1991). Furthermore, urine odor could be possibly used in diagnosing some diseases which is covered more in Chapter 5. It has been shown that multiple chemical classes such as acids, alcohols, ketones, aldehydes, amines, N-heterocycles, O-heterocycles, Sulphur compounds, steroids and hydrocarbons are found in VOCs of urine (Mills & Walker, 2001). Its formation is a result of gut microflora processing tyrosine – a non-essential amino acid (Bone et al., 1976). Moreover, certain VOCs could pose as biomarkers of certain diseases and as well work as a diagnostic tool. For example, some metabolic disorders related to diabetes, when present at high concentrations (Liebich, 1975).

However, many compounds are still not fully understood, and it is needed to research them more extensively.

As manifested above, human body odor profile forms by different odorants and in their diverse interactions. Most distinctive and studied body odor comes from bacteria breaking down particles excreted by exocrine skin glands, found mainly in the axillary area, anogenital region, and soles of the feet. Nonetheless, especially in the studies regarding diseases and illnesses, breath and urine odors are important to study as well, especially in their relation to VOCs analysis and potential diagnostic tools discussed further in Chapter 5 of the thesis. Both qualitative and quantitative differences in individual human body odors are influenced by an array of genetic and environmental factors which are presented in Chapter 2.

2. Factors Influencing Human Body Odor

Every human has a unique, distinctive body odor which seems to be relatively stable over time (Penn et al., 2007). Nonetheless, its individuality is a result of various factors including genetics, environment, and cosmetic products and their interaction. It has been researched that one's genetic makeup (Schaal & Porter, 1991), sex (Penn et al., 2007), age (Mitro et al., 2012), hormones and reproductive status (Havlíček et al., 2006), emotional state (Calvi et al., 2020), diet (Havlicek & Lenochova, 2006), smoking habits, health status (Shirasu & Touhara, 2011), fragrance use (Allen et al., 2019), or personality (Sorokowska et al., 2012) all shape the characteristics of human body odor.

Even though in reality it is quite problematic to strictly separate the effects of genes and the environment when discussing human body odor, as they both interact in various interdependent processes, throughout literature researchers often distinguish the factors to study the effects separately. In this work, it will be as well divided into the effects of genes and environment and cover the most significant and researched factors. Health factors will be separately discussed in Chapter 3, as they account for the main point of the thesis.

2.1 Genetic Bases of Human Body Odor

Some body odor specificity is attributed to genes and genetic makeup of an individual. Several studies concerning twins and kin recognition based on hedonic evaluation, but even chemical analysis of body odor precursors, or related to specific genes of MHC and ABCC11 support the notion that to an extent, body odor is determined by genetic factors.

2.1.1 Kin Recognition

One of the main indications comes from studies regarding the body odor of twins. Repeatedly, human conspecifics perceived the odors of identical twins as more similar compared to the odors of other participants. Moreover, correct matches occurred at rates better than chance and were similar to matches of the duplicate odors coming from the same individual. As these twins were non-cohabiting, the effects of shared environment were minimized and thus suggesting important influence of genetics. Dizygotic twins not sharing their genes entirely did not show the same pattern of body odor quality (Roberts et al., 2005). In addition, when sweat samples of monozygotic twins were chemically analyzed, it turned out that their patterns of acid precursors of body odors were noticeably more similar and stable between days and samples from both axillae in comparison to duplicate samples of participants repeatedly sampled in different days (Kuhn & Natsch, 2009).

Apparently, twins display significant resemblance of their body odors, but close relatives seem to have a similar odor as well. In a study by Porter et al. (1985) concerning mothers and their underaged children, unrelated individuals could correctly match odors of mothers and their children at rates higher than chance. However, to control for other possible environmental effects, another experiment was conducted. In the first experiment the argument could be that the correct matching of samples was due to the shared environment. But when garments of cohabitating husbands and wives and hence partners sharing the same environment and not the same genes were tested, no high levels of accuracy of matching the odors emerged. It shows that external influence alone is not sufficient to contribute to body odor similarity.

Also, the ability of within kin recognition of body odors shows a potential role of genes in odor specificity. Mothers who were in contact with their infant even for a short time in an interval from 10 minutes up to 1 hour were able to correctly identify their baby's odor in high percentages (Kaitz et al., 1987). Another test showed that also close kin relatives -fathers, aunts, grandmothers- recognized newly born children by their odor with little prior direct contact. At the same time, it must be added that learning the odors could play a potentially important role. For example, unrelated women towards an infant could in a relatively short time recognize body odor of infants they had spent some time prior to the testing at similar rates to those of the mothers (Kaitz & Eidelman, 1992).

When presented with odors, adult participants were able to recognize between the samples of their non-cohabiting full-siblings and strangers of the same age and sex. Both performed at rates higher than chance, but the study does admit the possibility of interplay of genetic and environmental factors (Porter et al., 1986; Porter & Moore, 1981). A more recent study found that fathers could not recognize the odor of their pre-pubertal and pubertal children better than by chance (Ferdenzi et al., 2010).

It seems that kin body odors have a uniquely identifiable resemblance and suggests that it is at least partially a result of genetic determination.

2.1.2 Major Histocompatibility Complex

Some evidence shows the role of major histocompatibility complex (MHC) genes in body odor and the possibility to perceive its gene variability by olfactory cues. MHC, in humans termed human leukocyte antigen (HLA), plays a role in immune processes in vertebrates and displays high polymorphism. This diversity could hypothetically have an advantage in combatting pathogen pressure, promote immunocompetence, and pairing with a partner with different MHC profile may reduce risks of inbreeding (Penn & Potts, 1999). Since studies with animal subjects showed relation between mate choices and MHC dissimilarity based on olfactory cues (Yamazaki et al., 1976), it was expected to find analogous tendency in humans as well (Havlicek & Roberts, 2009). Primarily, the research in humans regarding HLA focus on possible effects of HLA related odors on its attractiveness and consequent mate choice. However, the studies show mixed results and no final concluding statements might be presented yet. According to a recent metanalysis, a consistent preference for MHC-heterozygous individuals exists in mate choice, but no systematic preference for MHC-dissimilarity occurred (Winternitz et al., 2017). Effect of MHC-similarity on odor preferences was not found either (Havlíček et al., 2020).

The results of effect of HLA on mate choice is relatively mixed, and even chemical analyses did not show an effect of HLA-related genes on human axillary odor (at least not on odorous carboxylic acids), further tests between HLA complex and the human body odor perception must be performed.

2.1.3 ABCC11 Gene

Another relation between a specific gene and body odor was linked to the gene ABCC11 when axillary sweat was analyzed. The single nucleotide polymorphism (SNP) in the gene coding of transport protein ABCC11 was marked as crucial. Homozygous individuals in a SNP (538G>A) were characterized with less distinct axillary odor compared to those heterozygous, or with a wild type (GG) gene. The variation of gene ABCC11 is closely related to ethnicity, as the mutation of SNP 538G>A prevails in Asian population, and thus the formation of precursors that lead to typical axillary odor quality is minimal. The axillary odor of people with the variant could be described as faint and slightly acidic. Participants of European, African, or Pakistani descent without the change in the allele do show the characteristic axillary odor with its more intensive qualities (Martin et al., 2010).

Based on studies related to kin recognition, and HLA and ABCC11 related genes, an undisputed tendency exists that at least partially genes do influence the resulting body odor of an individual.

2.2 Environmental Influences on Human Body Odor

All the data above support the notion that human body odor signature is partly genetically mediated and influenced by genes. On the other hand, it must be added that other intrinsic and extrinsic factors play a key role as well and cannot be omitted. Current studies illustrate the effect of multiple environmental factors having an effect, but this chapter focuses on diet, reproductive state, and emotional state as these have been extensively researched and are considered to have significant effects. It must be noted that strictly speaking reproductive state, emotional state, or diet are not environmental per se.

2.2.1 Diet

Diet is considered as one of the primary environmental factors affecting human body odor. Foods such as garlic, mango, saffron, curry, fenugreek, red meat, beer, or asparagus have been shown to alternate breath odor, some demonstrate the effect on skin, or axillary odor. The role that diet plays in affecting human body odor firstly emerged in twin studies. Monozygotic twins could be distinguished from olfactory cues in cases they were on different diets, but not on the same diet (Wallace, 1977). Even trained dogs could discriminate between monozygotic twins on diverse diets, but not when they were on different diets (Hepper, 1988). Although, in a more recent study, dogs could distinguish the odors of monozygotic twins regardless of their environment or diet (Pinc et al., 2011). Still, these cases adequately exhibit the role of both genes and diet contributing to the final human body odor.

As expected, diet mostly affects breath odor due to salivary excretion of the compounds. It could be presented on the example of garlic which is constantly associated with unpleasant malodor (Amagase, 2006; Stevinson et al., 2000). Sulphur substances in garlic, or onions, more specifically, allyl methyl sulfide compounds were marked as responsible for a strong displeasing smell (Block, 1985). When breath was analyzed by an electronic nose, it was suggested that raw garlic has a strong odor and it intensifies and changes into unpleasant odor *in vivo* (Tamaki et al., 2008). In addition, the malodor lasts for a few hours, especially because breath odor is also derived from the processes originating in the digestive system as mentioned in the previous chapter (Suarez et al., 1999).

Garlic is not the only food studied in regard to breath odor. Ketogenic diet characterized by a reduction in carbohydrates and in an increase of protein and fat can include side effects like bad breath (Shilpa & Mohan, 2018). Sugary foods may as well result in a bad breath, as bacteria convert sugars to acid and change the oral environment (Aylıkcı & Colak, 2013).

In addition to the food people ingest, various drinks influence breath odor as well. For example, green tea seems to have a positive effect on breath odor by reducing aerobic mouth bacterial load and eliminating malodor (Moghbel et al., 2012; Zeng et al., 2010). On the other hand, alcohol results in an oral malodor. Especially daily intake is associated with bad breath and increases the risk of periodontitis (Suzuki et al., 2011).

The effect of diet on human odor was considered for axillary odor too. Perhaps counterintuitively, in a within-subject study, the consumption of raw garlic/garlic capsules had a positive effect on male odor quality as axillary odor was hedonically characterized as more attractive, pleasant, and less intense (Fialová et al., 2016). In a within-subject study focused on the effect of red meat, female raters characterized male donor's odors who had not eaten red meat in two weeks as more pleasant compared to the time when they had eaten it. The results indicate the consumption of red meat does influence the body odor of men (Havlicek & Lenochova, 2006). To the contrary, meat intake was considered to positively impact axillary odor in a study of Zuniga et al. (2017). It must be added that the studies used different methodologies, as in the latter the dietary data were self-reported and in comparison, the quantity of eaten meat was greater in the former experimental study. Thus, the difference implies the importance of the quantity of the eaten food. The study has also shown the impact of eggs, oils, and fats on odor pleasantness and negative influence of carbohydrates and seafood on male body odor (Zuniga et al., 2017).

Recently, a complete lack of caloric intake of women was tested in relation to body odor. Authors did not find a significant change in rating of pleasantness and attractiveness of the samples comparing usual caloric intake and the 48-hour long fasting period. Though, after all restrictions ended, the odors of women in the restoring period were characterized as more pleasant and attractive. It could be explained by eating less and lighter alternatives comparatively to their baseline regime (Fialová et al., 2019).

Urinary odor might be influenced by certain dietary choices as well. The urine samples of men who had ingested asparagus were subjectively assessed as pungent. It seems likely that the asparagus-related malodor is a result of molecules related to Sulphur containing compounds (Waring et al., 1987).

Undoubtedly, dietary choices do account for human body odor quality, attractiveness and intensity to an extent and could even shape interpersonal interactions, especially in the case breath odor in closer face-to-face situations.

2.2.2 Reproductive Status

It turns out, the body odors of women change across their menstrual cycle.

Numerous studies have shown women's body odor to be rated by men as more attractive and pleasant in the late follicular phase compared to other phases of the cycle. In addition, the differences stayed detectable even after seven days of the t-shirts kept at room temperature (Singh & Bronstad, 2001). Another, within-subject, carefully controlled study replicated those findings. Not only were men able to distinguish between odors of high and low fertility phases, but they also demonstrated above chance preference for high fertility odor samples (Gildersleeve et al., 2012; Havlíček et al., 2006). Possibly, levels of women's reproductive hormones estradiol and progesterone could explain the differences in body odor, as they predicted its attractiveness. Duringthe late follicular phase, when body odors are rated as most pleasant, estradiol levels are high, progesterone levels low. Congruently, women's body odors were rated as more attractive the lower their progesterone levels and the higher their estradiol levels were (Lobmaier et al., 2018).

In addition, changes in body odor in pre-reproductive and post-reproductive status have been perceived. As described in the previous chapter, body odor becomes more distinctive in puberty when apocrine glands activate, and hormonal changes occur. When mothers hedonically rated odors of their children, they characterized pre-pubertal scents as pleasant, whilst post-pubertal as more intense (Schäfer et al., 2020). On the contrary, apocrine glands decrease in function with age which could explain why odors of old age subjects were rated as less intense. Although, the odors of older-aged females were marked as less pleasant than those of middle-aged (Mitro et al., 2012). Not many studies focus on body odors of women after menopause, in a research article concerning mainly mood swings, the odors of older women were characterized as most unpleasant, intense, masculine, and oldest in age, even compared to old men (Chen & Haviland-Jones, 1999).

2.2.3 Emotional State

The effect of emotions on human body odor has been studied as well. Mainly the emotions of fear, stress, and anxiety have been shown to be hedonically recognizable by perceivers (Chen & Haviland-Jones, 1999).

Due to its potential evolutionary relevance and survival benefit, negative emotions of fear and anxiety are often recognized more than positive emotions and have been more researched. Although happiness is studied less frequently, it similarly reflects in human body odor. The emotions of fear and stress result in a more intensive body odor quality. Even though the subjects can often qualitatively distinguish between the smells of different emotions, they cannot correctly match an odor to the original emotion (Iversen et al., 2015). Possibly, it could have an effect only on subconscious levels.

The effect of emotions is not only expressed by hedonic evaluation, but it also reflects in the physical reactions and facial expressions. For example, female raters exposed to happy odors of male donors generated a happier facial expression compared to the odors of the controls (de Groot et al., 2015). In another experiment, female participants exposed to odor of male fear tended to change their facial expressions into a more fearful one (de Groot et al., 2012).

Furthermore, brain scan studies showed that individuals smelling the samples of donors who endured emotionally stressful event, showed brain activity in regions processing emotions demonstrating that odor of a fear works as a cue that is processed by the brain (Mujica-Parodi et al., 2009).

All examples seem to support the notion that emotion can impact human body odor. However, the results on human ability to correctly identify them based on odor and correctly match them at rate above chance are mixed. Potentially, they could be detected, at least on a subconscious level and have behavioral, or cognitive consequences.

This chapter introduced diet, reproductive state, and emotional state to illustrate how environmental factors may impact human body odors. For the purposes of this thesis, it is key to describe if and how diseases and illnesses may impact body odors, hence in the following chapter, health status' impact is discussed in more details.

3. Health Status

Throughout history, it has been well observed that some changes in health status are correlated with changes in human body odor. For example, in the 5th century BD the Greek physician Hippocrates associated certain diseases with specific odors of urine, breath, or sputum (Adams, 1994). In the 11th century, the Arab physician Avicenna diagnosed his patients by perceiving changes in the smell of urine. Even 19th century medics were taught to diagnose physical conditions by their smell (Porter, 1994). Over time, with advances in medicine, doctors renounced from using odors in diagnostics. However, in multiple cases, even more recently, odors have been solid indicators of illnesses and diseases and guided researchers to gain insight within the topic and helped them to correctly diagnose multiple patients (Centerwall & Centerwall, 2000; Hayden, 1980; Smith & Strang, 1958). It turns out that possibly with advances in technology and awareness of the topic, odors of diseases could again serve as quick, non-invasive, and perhaps cheap tools in disease diagnostics.

Indeed, contemporary research has shown that infections, metabolic disorders, tumors, toxin exposure, and even psychiatric disorders may influence human body odor by altering the normal VOCs ratio, or by producing new VOCs altogether. Several examples of some of the most prevalently described illnesses and diseases with their impact on human body odor are presented below.

3.1 Metabolic and Genetic Disorders

It was shown above genes are partially responsible of an individual's body odor. Unsurprisingly, a genetic change, malfunction, or disorder may have an impact on the resulting body odor. Genetic and metabolic disorders are characterized by either deficiency in enzymes, or transport system defects. As a result, specific metabolites accumulate mostly in blood and urine, but possibly also in the breath, or other body fluids. High concentrations of metabolites lead to the detection of the disease. In some cases, these metabolites produce VOCs which could lead to characteristic body odor. Most metabolic disorders are highly heritable and if left untreated, they could lead to irreparable damage, or be even lethal.

Phenylketonuria is an inherited autosomal recessive disease related to the deficiency of phenylalanine hydroxylase. Normally, this enzyme converts the amino acid phenylalanine into tyrosine. However, due to its deficiency, phenylalanine accumulates in blood and is metabolized into phenylpyruvic acid and phenylacetate, both harmful to the brain. Phenylacetate exuded in urine and sweat is linked to cause a musty, sweaty malodor resembling locker rooms (Burke et al., 1983). Nowadays, newborns are screened for phenylketonuria, but in the past, the first patients were diagnosed thanks to olfaction – as mothers of concerned children reported the urine to have a strange musty odor (Centerwall & Centerwall, 2000).

Isovaleric Acidemia is an inherited autosomal metabolic disorder caused by a deficiency of the isovaleryl-CoA dehydrogenase which is involved in processing amino acid leucine. When leucine and its derivatives cannot be metabolized, they accumulate in the blood and could be damaging for the central nervous system. Different levels of the leucine derivatives could result in a specific body odor characterized as “cheesy”, acrid, or to smell like “sweaty feet” (Tanaka et al., 1966).

Maple syrup urine disease is a metabolic defect due to which individuals cannot break down branched-chain amino acids (valine, leucine, isoleucine) through oxodecarboxylation. It is caused by the deficiency of the enzyme 2-oxo acids dehydrogenase complex. As a result, branched-chain amino acids (proteins found especially meat, dairy products, and legumes) accumulate in blood, tissues, cerebrospinal fluid, and urine. If untreated with special dietary restrictions of branched-chain amino acids, or episodes of acute metabolic decompensation, it leads to mental retardation and cerebral degeneration (Liebich, 1975). It results in a recognizable unique smell similar to caramelized or burnt sugar, or maple syrup found in sweat, urine, or in earwax (Menkes, 1959).

Patients suffering from a rare autosomal metabolic disorder trimethylaminuria cannot oxidize dietary-derived malodorous trimethylamine (TMA) to trimethylamine Noxide by an enzyme in the liver (Zhang et al., 2003). TMA is the product of gut bacteria metabolizing food rich in choline like eggs, legumes, or organ meat. Consequently, TMA stays unmetabolized in the body and is excreted in sweat, breath, urine, saliva, and even reproductive fluids. As TMA is a gas and characterized by a pungent rotten-fish malodor, the body's inability to correctly metabolize it results in an unpleasant fish-like human body odor (Arseculeratne et al., 2007; Chalmers et al., 2006).

Cystinuria is an autosomal recessive genetic disorder that affects reabsorption of the amino acid cystine. Under normal circumstances, it is excreted in urine, however, in some cases it cannot be dissolved and forms crystals. These accumulate in the kidneys, urethra, and bladder. The urine of some patients might have a characteristic rotten-egg odor, as cystine contains Sulfur (Bondy et al., 1980).

Tyrosinemia is a metabolic disease when individuals cannot break down the amino acid tyrosine. Three types of tyrosinemia exist, with type I being the most severe. Tyrosine uncontrollably accumulates in the body. The symptoms begin to show in the first few months of the infant's life and include failure to gain weight or grow. They may show yellowing of the skin, tendency to bleed and offput a recognizable cabbage-like odor (Bondy et al., 1980).

Diabetes Mellitus occurs when pancreas fails to produce proper quantities of insulin, a hormone responsible for transporting glucose (the main source of energy for our body) into the body's cells. The most prevalent types of diabetes are type I, type II, and gestational diabetes which could develop in some pregnant women. Sometimes the causes of diabetes are unknown, but it could be caused by viral infections, or life-style management (obesity, high stress levels, or alcohol intake). In diabetes type I, insulin producing pancreatic beta cells are destroyed. Hence, no insulin is produced. If left untreated, diabetes type I may lead to ketoacidosis which occurs when high levels of ketones are in the blood. Since no glucose enters the cells and they still need energy, the body starts burning fatty acids and produces acidic ketone bodies as by-products. Those are excreted in the patient's breath and urine which have a fruity, sweet, rotten apple-like odor. Its odorous qualities have been linked to one of the ketones produced – acetone (Manolls, 1983; Shirasu & Touhara, 2011).

3.2 Infectious Diseases

In many cases, infection causing pathogens might change personal body odor. Multiple VOCs are produced because of interactions between host organic media and microbial toxins. Those volatiles are usually released in breath, skin, sweat, vaginal fluid, urine, and feces. However, the effect of infections on human body odors are more complex compared to metabolic disorders, and hence more demanding to study and characterize. Some of the reasons might be that microbial species can metabolize in diverse way producing a wide range of VOCs, often certain bacteria produce similar VOCs to other bacteria, and infectious diseases might comprise of multiple infections that lead to a specific odor once, but not the next time (Havlicek et al., 2017). Nonetheless, several infections have been associated to distinctive body odors. Mostly, odor changes are recognized in bacterial infections, but viral infections could have an impact as well. Below, several infectious diseases are introduced to illustrate their impact on human body odor, whether it is breath, skin odor, or urine.

Tuberculosis is a disease caused by *Mycobacterium tuberculosis* which mostly affects the lungs but could potentially damage other parts of the body. Patients suffering from tuberculosis were reported to have foul breath odor. Moreover, a specific VOC breath profile has been reported in infected individuals, potentially showing biomarkers of tuberculosis (Syhre & Chambers, 2008).

Diphtheria is another respiratory infection, caused by bacteria *Corynebacterium diphtheria* resulting in a sore throat. It has been linked to a sweetish, putrid breath odor (Hayden, 1980).

Scarlet fever is caused by bacteria *Streptococcus pyogenes* leading to sore throat, fever, and red-colored skin and tongue. Individuals may have a specific foul odor of their breath and skin (Honig et al., 2003).

Cholera is an intestinal infection by bacteria *Vibrio cholerae* which causes dehydration, vomiting and watery diarrhea. The stool of individuals with cholera is referred to have a rice-water consistency and sweetish odor. One analysis suggested pmeth-1-en-8-ol and dimethyl disulfide as VOCs potentially responsible for the smell.

Whilst dimethyl disulfide was characterized to have an unpleasant odor, p-menth-1-en8-ol has a pleasant odor (Garner et al., 2009).

Variola virus causes smallpox, characterized by symptoms of fevers, headaches, vomiting, and puss-filled rashes all over the body. When infected and opened, the rashes emanate a pungent, sweetish oppressive smell (Tucker, 2002).

Typhoid fever is a serious infection of the intestinal tract primarily caused by a bacteria *Salmonella Typhi*. Its signs usually include headaches, high fever, stomach pain and other digestive problems. The skin odor of infected people is characterized as musty or having a freshly baked brown bread quality (Hayden, 1980).

Yellow fever is a disease spread through mosquito bites. The symptoms include fever, muscle aches, headache, backache, or vomiting. It has been reported that patients suffering from yellow fever smell like a "butcher's shop" (Hayden, 1980).

Bacterial vaginosis occurs with the overgrowth of certain bacteria in resident vaginal microflora. Usually, it is diagnosed when three out of the four following symptoms occur: when vaginal discharge occurs, vaginal fluid pH > 4 5, vaginal epithelial cells are covered with bacteria, fishy odor is released. Cheesy or fishy odor is often associated with bacterial vaginosis. It is due to bacterial reduction of trimethylamine oxide to trimethylamine in vaginal secretion (Wolrath et al., 2002). However, it must be noted that not all women with bacterial vaginosis report vaginal malodor (Sonnex, 1995).

Even malaria, a serious mosquito-borne infectious disease seems to emit a specific odor. Mainly it has been tested on mosquitoes who tend to show a greater preference for individuals infected with a parasite. The researchers work with manipulation theory – malaria parasites alter the phenotype or behavior of their host to increase transmission success and fitness. In case of malaria, they may want to become more attractive to mosquitoes by altering the smell. It could be a functional strategy, because for mosquitoes, olfactory cues play a significant role in host-seeking. In line with the theory, mosquitoes were more attracted to infected children. After antimalaria treatment, mosquitoes were less likely to be drawn towards the subjects (Busula et al., 2017; Lacroix et al., 2005; Robinson et al., 2018).

3.3 Cancers

Cancer involves abnormal cell growth which can affect any part of the body. More than 100 types of cancer exist. However, mostly, lung breast, colon, prostate, skin, and stomach cancer prevail and account for millions of yearly deaths (WHO, 2021). The fact that cancer might have a distinctive smell is mostly supported by studies performed with dogs, but also the analysis of breath, urine, or blood of patients shows the possibility of detecting specific VOCs related to cancer. When evaluating the breath of patients with lung cancer a trend of specific VOCs appeared and included alkanes (Phillips et al., 2003). Also, the breath of women suffering from breast cancer appeared to contain a set of VOCs that could identify them (Phillips et al., 2010). The specific VOCs differ among studies, but in case of *in vitro* experiments, the results seem to be promising. In lung cancer, four specific VOCs were identified (heneicosane, dodecane, 2-ethyldodecanol and decanal), with a suggestion they could be lung cancer-related biomarkers (Thriumani et al., 2018).

In addition, canines can be trained to detect cancerous odors with high rates of specificity (ability to correctly identify those without the disease) and sensitivity (ability to correctly identify those with the disease). A trained dog could correctly distinguish between ovarian carcinomas and healthy tissues suggesting a carcinoma-specific odor (Horvath et al., 2008). It is suggested even plasma samples of patients with ovarian cancer emit specific VOCs, as trained dogs could detect it (Horvath et al., 2010). Bladder cancer odor from urine samples was also detected as rates higher than chance suggesting characteristic VOCs (Willis et al., 2004). Moreover, it has not been yet fully understood whether dogs could directly detect odors related to cancer, or the accompanying inflammatory phenomena. Nevertheless, the studies support the premise that various types of cancers do have an odor, although no human subjects have been tested if they could distinguish between samples as well. Diagnosing cancer by dogs is further discussed in Chapter 5 on diagnostics.

3.4 Toxin Poisoning

According to several cases from emergency departments, intake of toxins can alternate body odor. Even though, many toxic substances are odorless, some do potentially indicate poisoning by their odor. Cyanide poisoning may lead to breath odor smelling like bitter almonds. Arsenic, organophosphates (used as pesticides), selenium, or phosphorus could lead to garlic-like body odor. Ingestion of isopropyl alcohol, acetone, or amyl nitrate results in a fruity odor in one's breath (Behrman & Goertemoeller, 2009; Hayden, 1980).

3.5 Psychiatric Disorders

Among psychiatric disorders, schizophrenia has attracted most attention in regards of emitting a specific smell. Schizophrenia is a serious mental disorder in which affected individuals have cognitive defects and relate abnormally to reality. Disordered thinking and behavior, hallucinations and delusions are some of the prevalent symptoms of the disease. Firstly, based on anecdotal experience that psychiatric wards have a distinctive foul smell, it was thought that patient suffering from schizophrenia could emit a characteristic odor. In the 1960s, trained rats could identify the odor of sweat of certain schizophrenic patients. Thereafter, the smell of schizophrenia was attributed to trans-3methyl-2-hexenoic acid (TMHA) (Smith et al., 1969). Later study showed no specific relation between TMHA and schizophrenia, as it could be identified with subjects without schizophrenia as well (Gordon et al., 1973). It appears TMHA cannot be considered as a reliable marker of schizophrenia, but a tendency of higher concentration in schizophrenic patients does exist. Furthermore, higher levels of carbon disulfide (neurotoxin) and pentane were found in patients' breath analysis (Phillips et al., 1993). Also, VOCs pattern recognized in schizophrenics included 11 specific compounds (Phillips et al., 1995). Nevertheless, according to gas chromatography-mass spectrometry analysis, the odor shows a different composition, suggesting its different quality compared to non-schizophrenics (Di Natale et al., 2005). Further studies are needed to clarify the relation between characteristic odors, VOCs, and schizophrenia. Nonetheless, the possibility of mental disorders having an impact on human body odor cannot be disregarded altogether.

As it was demonstrated in the previous chapter, emotional state shows tendencies to alternate body odor. In that case, potentially, affective or mood disorders, especially anxiety or depression could alternate body odors too. More research within the field, especially focusing on psychiatric, mood and affective disorders would be beneficial.

3.6 Parkinson's Disease

This progressive nervous system disorder affects the brain, and typically manifests itself in tremor, slower movement, stiffness of the muscles and general impaired balance and coordination. Symptoms of depression, urinary problems, sleep disruptions may occur as well (Davie, 2008). Recently, another symptom has been added to the list, as reportedly Parkinson's disease is accompanied by an unpleasant yeast smelling odor. It was brought to attention by Joy Milne, a woman who turned out to have an unusual sense of smell. After media coverage, others have come forward to confirm Joy's findings, it has not been tested if they can detect the odor too. At first, she detected a greasy musty smell of her husband, but later at a support group for Parkinson's disease patients she realized that all had the same smell – some less, some more intensive. Her peculiar hyperosmic abilities were tested and she identified the smell to be most localized on the upper back, not the axillae (opposed to expectations and the fact that in research axillary odor is mostly used). More specifically, the odor was associated with areas of high sebum production (Morgan, 2016). In an experiment combining Milne's abilities and the technology of thermal desorption−gas chromatography−mass spectrometry - chemicals hippuric acid, perillic aldehyde, eicosane, and octadecanal were detected as potential contributors to the musky smell of Parkinson's (Trivedi et al., 2019).

Above, it was demonstrated that health status does have an impact on human body odor. Not all processes responsible for body odor alteration in illnesses are fully understood and not all specific disease-related VOCs have been identified. Nonetheless, clearly infectious diseases, metabolic disorders, neurodegenerative disorders, tumors, poisoning and possibly psychiatric disorders in a way alter body odor and often result in a distinctive foul (must be mentioned that sweet, or bread-like smells occur as well) scent emanating from skin, breath, urine or anogenital region.

But do these specific odors of ill people influence their conspecifics?

4. Behavioral Immune System

Above, some illnesses and disorders were introduced and discussed in terms of modern contemporary scientific research. However, pathogens have always been a threat, especially for socially living organisms with high population density, with humans not being an exception. Throughout evolution, infectious diseases have likely caused more deaths in humans than any other harmful causes combined (Inhorn & Brown, 2013). Simultaneously, vertebrates - including humans - have developed a set of complex reactive mechanisms to protect the host from infections, known as the physiological immune system (PIS) (Janeway, 2001). Its role is to detect the presence of variety of pathogens, distinguish them from the organism's own healthy tissue and consequently mobilize a response to eliminate the infectious agent. Even though, the immunological response is very effective, it is also highly costly both energetically and nutritionally. It could limit the individual in the processes of growth, reproduction, or thermoregulation which are crucial for the organisms' proper functioning (Lochmiller & Deerenberg, 2000; Sheldon & Verhulst, 1996). In addition, physiological immune system is reactive and defends the organism only after the pathogens had struck (Schaller, 2011).

Thus, researchers have proposed an existence of behavioral immune system (BIS), which is a complementary set of psychological mechanisms beneficial for the organism that would inhibit direct contact with pathogens before even entering the body. More specifically, BIS has been defined as a set of complex perceptual, affective, cognitive, and behavioral mechanisms which is activated in a response to certain perceptual cues to avoid potential risks of pathogen exposure and hence save the organism's energy (Ackerman et al., 2018; Schaller, 2011).

Nevertheless, these two systems are not strictly divided, on the contrary, it is thought that they are interconnected and work in conjunction. In humans, it has been demonstrated that the feeling of disgust (the main emotion associated with BIS) elicited an increase of immune markers in their oral cavities (Stevenson et al., 2011). In addition, individuals presented with pictures portraying disease-connoting characteristics had higher levels of pro-inflammatory cytokine interleukin-6 in their organism following in vitro LPS stimulation (Schaller et al., 2010).

Some types of defensive behavioral responses have been observed among different animal species. For example, wood ants brought solidified coniferous resin to their nests which protected them against harmful microorganisms (Chapuisat et al., 2007); or Gombe chimpanzees acted hostile towards conspecifics infected with polio (Goodall, 1986). Moreover, female mice showed aversion towards the odors of urine of males infected with parasites, and rather stayed in the vicinity of the odors of healthy male counterparts (Kavaliers & Colwell, 1995). However, its importance and implications have been also studied for human health, psychology, and culture.

As mentioned, BIS consists of a set of interconnected mechanisms that at first detect pathogen-connoting cues in the environment which then employ disease-relevant affective and cognitive structures in working memory and consequently facilitate a behavioral response – for example, avoidance of the pathogen.

4.1 Perceptual Mechanisms of Behavioral Immune System

For BIS to function it must involve certain detection principles that are sensitive to pathogen presence. Since most are directly unrecognizable at plain sight, various perceptual cues related to pathogen presence must be used. BIS employs visual, tactile, auditory, olfactory sensory modalities, as well as their interaction to detect stimuli in the environment that could potentially pose some risk. The stimuli could include threatening objects like feces, or vomit, or conspecifics presenting disease-related cues, or behaviors carrying high risks (promiscuity, poor hygiene).

4.1.1 Visual Perception

Visual perception of disease connoting cues in humans is regarded as most viable. Stimuli from the environment like feces and vomit, but even social cues like skin lesions, or morphological deformations are instantly and easily visually recognizable. When it comes to the human health status, visual cues including paleness of the skin and lips, redness of the eyes, swollen face or hanging eyelids influence health perception (Axelsson et al., 2018; Henderson et al., 2017). For example, individuals presented with a series of photographs showing a potential disease threat were assessed as more disgusting than similar photographs without disease connotation (Curtis et al., 2004). In addition to static face pictures, even body motion of LPS-injected individuals in video clips showed a small, but persistent trend to be rated as less healthy contributing to the importance of visual cues when perceiving an illness (Sundelin et al., 2015).

Another study creating an instrument for testing visual disgust has clearly indicated that certain stimuli portraying scenes and events highly salient of pathogen presence (e.g., feces, rotting masses, insects in food/wounds, vomit) are rated as more disgusting compared to more neutral ones (e.g., pasta, feet, hands, toilet, sanitary products) that were visually similar but did not have a disgust trigger (Culpepper et al., 2018). Furthermore, as already previously briefly mentioned to illustrate the link between BIS and PIS, in participants exposed to pictures of people expressing disease-connoting characteristics their PIS activated and they produced higher levels of the proinflammatory cytokine interleukin-6 compared to the group exposed to pictures of guns (stressful psychological experience), or neutral stimuli (Schaller et al., 2010). Human vision clearly helps to identify potentially threating stimuli, even from greater distance and plays a role in BIS.

4.1.2 Tactile Perception

Touch perception solely works on direct contact with the stimuli and potentially presents a higher chance of exposure to risk, in contrast to the other modalities working at greater distances which could be safer for the individual. But the sense of touch enables people to detect various qualities of the given stimuli in detail, including moisture, consistency, or temperature. Since many pathogens thrive in moist, warm, and dark conditions, but they also play a role in breakdown of the tissues and hence those conditions are a result of their action. Therefore, tactile modality could provide information about potential pathogen presence.

When tested, participants indeed rated wet stimuli and biological-like consistency stimuli (dough) more negatively compared to dry stimuli and inanimate-like consistency stimuli (rope). It shows that moisture and biological-like consistency are rated as more disgusting possibly due to the presence of pathogens (Oum et al., 2011). Moreover, when tactile properties were analyzed more specifically, sticky, and wet textures strongly correlated with disgust. The context of the tested stimuli was key, as participants who believed to touch objects possibly related to disease showed highest disgust rating compared to the other groups (Saluja & Stevenson, 2019). Hence tactile cues seem to have a part in pathogen detection and activate BIS.

4.1.3 Auditory Perception

In the current research, the sense of hearing is perhaps least covered in research in regard to perceptual cues related to diseases. Most likely the sounds made by other conspecifics like the sounds of sneezing, vomiting, or coughing could be important as easily distinguishable cues marking pathogen threat in the close environment from a distance. When tested, participants could not correctly identify the sounds of diseases compared to control sounds. The tendency of the participants was to mark the sounds they considered as more disgusting to be infectious in their origin, regardless of its true origin. People seem to react rather negatively to the sounds of diseases but cannot recognize their origin (Michalak et al., 2020).

4.1.4 Olfactory Perception

Olfactory modality is often related to detection of spoiled food or dubious environments. To illustrate, people tend to react negatively to odorous meats, or milk, and avoid places with feces, or decaying bodies. Furthermore, olfactory cues can often be detected from distance without getting into direct contact with the pathogen source (Schwambergová et al., 2020). As already described in Chapter 3, also some diseases have an impact on human body odor. From the point of BIS, odors of diseases emanating from humans might be significant cues for recognizing pathogens.

To study it, Olsson et al. (2014) injected individuals by lipopolysaccharide (LPS), an endotoxin causing an inflammatory response simulating a disease-like effect. When assessed, the axillary body odor of LPS-injected subjects was indeed perceived and rated as more intense and less pleasant compared to the healthy and placebo groups. The results of perceptual ratings were not replicated in Regenbogen et al. (2017) in which body odors of LPS-injected subjects were not assessed as more unpleasant and intense than the healthy ones. Possibly, it could be explained by using different methods, as the body odors were presented from head-space saturated jars in Olsson et al. (2014) and by an olfactometer in the latter. The former uses glass jars containing odorants which are presented to the raters. The latter is an instrument that presents odor stimuli in a standardized computer-controlled manner with determined duration, concentration, or air flow (Al Aïn & Frasnelli, 2017). Usually, odors from olfactometer are perceived as less intense. Nonetheless, it was demonstrated that disease-related olfactory cues are processed by cortical networks in the brain and shows its possible effect at non-conscious levels (Regenbogen et al., 2017).

Previously, the effect of diseases on urine odor was discussed (e.g., maple syrup disease) and it seems to be a potential source for disease-related olfactory cues. Hence, the effect of LPS-induced inflammation on urine odor was tested. The results indicated acute inflammation had an effect on urine odor that was detectable by human and chemical assays. A tendency to perceptually view the inflammatory urine samples as more aversive compared to healthy samples appeared. In the chemical assays, differences in abundance of acetophenone and pyrrole were detected, but no causal links were induced. In summary, the continuing evidence of inflammatory processes impacting human body odor being perceptually distinguishable strengthened (Gordon et al., 2018). Although, olfactory cues related to the smell of urine might be important in activating BIS in certain marginal situations, mostly, in usual social interactions the odor of urine could be considered as negligible.

The LPS model can demonstrate humans' ability to detect cues of acute inflammation and bypass confounding variables including medication and lifestyle changes that are often associated with natural sickness model and could potentially influence body odor. However, some criticize its ecological validity and call for testing with naturally occurring illnesses. Hence, the effect of odor cues of naturally occurring respiratory infections like cold and the flu was researched. In that case, no effect in conscious perception and consequent ratings of the illness-related body odor was observed. Although, a tendency to perceptually detect infection-related odors and rate them as unpleasant and aversive emerged, no statistical significance difference was recorded. According to the authors, the difference in the resulting effect between the natural sickness model and the LPS experimental model could stem from the individual course of the illnesses. Although, both lead to inflammatory responses, in the study, only mild symptoms were reported by the subjects suffering from the flu, or cold. Whilst the LPS-injected subjects in other studies had more severe symptoms, headaches, or higher degree of fever. Thereby, harsh symptoms, or advance stage of the illness could impact the strength of the disease-related olfactory cues (Sarolidou et al., 2020b).

Even though, the results are mixed, the notion that sick individuals emit chemical cues detectable by others and are thereafter rated as unpleasant and more intense has been apparent.

4.1.5 Multimodal Perception

Naturally, at most time perceptional cues are not presented separately in a real life environment. Therefore, some studies used a multimodal approach and tested both visual and olfactory disease-related cues at the same time. Facial pictures of LPS-injected subjects together with sick body odors had the tendency to be rated less desirably and it showed increased neural activation in face and odor perception networks demonstrating an effect of multisensory integration model of disease-related cues (Regenbogen et al., 2017). Similar results were found when participants were presented with the face and odor of sickness (again induced by LPS injection), the liking of them decreased compared to healthy controls (Sarolidou et al., 2020a).

As people often use more than one, or two senses at a time to perceive their environment, it is important to study integration of the senses in the process of detection of disease-related cues to activate BIS, and perhaps to study which sense plays a bigger role compared to the others.

When lay beliefs of people were tested which senses are accurate and effective in identifying pathogenic threats, sight was always prioritized. The studies showed that sight and sound were considered relevant and likely to be used in interpersonal communication (identification of the sick), while sight, smell and taste were prioritized in food identification. However, taste was less preferred to be used - it seems that people rather use less effective but safer sensory information (Ackerman et al., 2020).

4.2 Affective Mechanisms of Behavioral Immune System

Usually, with the detection of disease-related cues, disgust is elicited which is considered the central emotion related to BIS. Disgust has been defined as an experience of repulsion, possibly followed by nausea, and a strong feeling to avoid the eliciting stimulus. In addition, it could be accompanied with specific facial expressions including slightly narrowed brows, wrinkling of the nose, or a curled upper lip (Oaten et al., 2009). Autonomic responses like a reduced systolic blood pressure, heart rate changes and decreased skin conductance may also follow (Croy et al., 2013). Currently three main domains of disgust are used throughout literature - pathogen disgust (disease avoidance) and derived domains of sexual (negative affective reaction to certain sexual partners and practices) and moral (negative affective reaction to social norm violation) disgust (Oaten et al., 2009; Tybur et al., 2009). The main proposed function of disgust is disease avoidance. Hence, all the perceptual disease-related cues mentioned in chapter 4 should cause the emotion of disgust.

Those who were presented with visual stimuli of images related to potential pathogen presence involving food, animals, bodily products, injuries/infections, death, and poor hygiene rated the stimuli as more disgusting compared to neutral stimuli (Culpepper et al., 2018; Val Curtis et al., 2004; Haberkamp et al., 2017). Tactile cues having moist, sticky, and biological-like consistency were found to induce disgust in tested participants too (Oum et al., 2011; Saluja & Stevenson, 2019). Even auditory cues may induce the emotion of disgust. Subjects presented with disgust-inducing auditory stimuli showed a change in physiological markers. They tended to have enhanced systolic blood pressure and increased skin conductance compared to controls (Croy et al., 2013). However, neuronal responses to auditory disgust elicitors produced only small activation changes, possibly meaning its reduced importance in disgust perception (Phillips et al., 1998).

Most importantly for the thesis, olfactory cues could possibly have a potential to induce the emotion of disgust and one of its main function could be avoidance of hazardous stimuli including microbial threats in the environment (Stevenson, 2009). For example, the odor of vomit was uniquely associated with disgust (Glass et al., 2014). Or, when students were presented with methyl methacrylate (acrid, repulsive odor) and propionic acid (odor resembling body odor sweat) they evoked disgust in their verbal response, but anger in the autonomic (unconscious) response (Alaoui-Ismaïli et al., 1997). In another approach, when participants were asked to list odors that evoke different kinds of emotions, almost all were able to name an odor that makes them disgusted falling into the class of death and waste (e.g. feces, vomit, organic waste) (Croy et al., 2011).

The capacity of odors to induce emotions, including disgust is frequent. However, no direct evidence showing the emotion of disgust as a reaction to human body odor and more specifically to body odor of diseases has been presented in the current research. The odors of some illnesses do impact human body odor and may serve as olfactory cues activating BIS, as they are perceptually recognizable and could induce disgust. As outlined in the previous chapter, the axillary odor and urine odor of subjects injected with LPS were rated as more intense, less healthy and unpleasant (Gordon et al., 2018; Olsson et al., 2014). In addition, the axillary odor of men suffering from acute stage of gonorrhea was perceptually judged as unpleasant by women raters (Moshkin et al., 2012). However, it must be added the results are mixed, and no significance in disgust ratings of the odors of respiratory infections was found (Sarolidou et al., 2020b).

On one hand, in some cases the stimuli were only rated as more intensive, negative, unpleasant, without any evidence of eliciting the emotion of disgust. Therefore, the need to be cautious and not coming to hasty conclusions is crucial. On the other hand, it was illustrated by numerous studies that various pathogen-related cues induced disgust in tested participants. Nevertheless, without being redundant, the tendency to rate some disease-related olfactory cues as unfavorable is apparent.

4.3 Cognitive Mechanisms of Behavioral Immune system

Once the perceptual cues connoting pathogens in the environment are perceived, psychological response is activated. It includes the arousal of emotional experience – the formerly mentioned disgust, but also the activation of specific cognitive structures that consequently enable behavioral response. Disgust may motivate an impulsive avoidant response, but alone cannot cause planned actions like an effort to quarantine or social exclusion which reduce long-term threats of pathogen effected individuals. The deliberative cognitive processes of BIS allow people to realize potential threats after detecting pathogen-related cues and facilitate consequent behaviors. These processes even let individuals to empathize with those who are suffering from an illness, or are disabled, instead of employing avoidance behavior (Pryor et al., 2004).

For example, mothers tended to have lower disgust sensitivity compared to non-mothers when presented with pathogen disgust and visual disgust domains and do not seem to employ avoidance behavior in taking care of their offspring (Prokop & Fancovicova, 2016). In healthcare professions disgust sensitivity plays a significant role as well. According to data from a study based in New Zealand, students who enrolled in courses targeted at medical careers (higher exposure to elicitors of disgust) showed lower levels of disgust sensitivity compared to students in pharmacy, but data comparisons to other non-medical professions were absent (Consedine et al., 2013). However, in the field, professionals often experience disgust which leads to decrease in their empathy and emotional exhaustion (Goerdeler et al., 2015; Ostaszkiewicz et al., 2016). Nonetheless, the way to overcome it is to employ cognitive structures, stay empathetic and familiar with the patients, or perceive them as nice, because the power of reframing is often strong (Dongen, 2001; Jackson & Griffiths, 2014).

Moreover, the cognitive mechanisms in BIS are differently applied in children who often do not understand what events, or stimuli might pose pathogen risk. For example, children before the age of 2 will put almost anything into their mouths. Infants and young children are often tolerant to odors of disgust and decay which are disgusting for adults (Engen & Corbit, 1970). Only after the age of 8 are children able to reason why certain objects are disgusting. It seems that disgust is not present in infants and young children and develops over time (Rozin & Fallon, 1987). Current studies are done mostly with adult participants, and it is unknown how children would perceive olfactory cues related to disease and illnesses. Based on the above-mentioned results, their reaction to odor stimuli could be different and could show whether experience with different smells and learning is necessary. Perhaps, children might smell the disease-related odors as less pungent and would not mark them as unpleasant.

4.4 Behavioral Mechanisms of Behavioral Immune System

The behavioral component of BIS can either be reactive or proactive. Reactive mechanisms follow the presence of pathogen connoting information posing an immediate risk. They mostly take the form of avoidance behavior which should consequently reduce the risk of infection. However, in current research, behavioral responses themselves are not directly studied in any modalities concerned, at least not in humans. When it comes to olfactory modality, avoidance behavior was well-observed in studies of rodents whose body odors alter due to numerous infections, similarly to humans. Based on olfactory cues, rodents can distinguish infected individuals and display aversive and avoidant behaviors towards them (Kavaliers et al., 2005). For example, LPS injected adult male rats released aversive odor which caused increased avoidance of conspecifics (Arakawa et al., 2009). When female mice were infected with larvae of *Trichinella spiralis*, male mice had lower tendencies to mount and copulate with infected females (Edwards & Barnard, 1987). On the other hand, male rats infected with tapeworm *Hymenolepis diminuta* were avoided by female rats (Willis & Poulin, 2000).

Avoidance behavior in humans when exposed to the odors of diseases has not been researched yet. One might only speculate that based on decreased preferences and unpleasant ratings of illness-related smell, it would similarly as in rodents lead to avoidance behavior. Though, possible impact of malodorous cues on human behavior was researched in relation towards condom use attitude. Students exposed to fecal smelling chemical expressed greater intensions to use condoms compared to controls which suggests that olfactory pathogen threat could induce behavioral changes (Tybur et al., 2011). It should be added, the results were only based on self-reporting and real-life behavior of participants was not recorded.

On the other hand, proactive responses are employed to manage the long-term risks of contracting a disease or an illness. They include habits like hygienic behavior to proactively reduce risks from persistent threats of bacteria and viruses that turned out to be motivated by the desire to avoid and remove disgusting things (Curtis & Biran, 2001).

4.5 Social Implications of Behavioral Immune system

BIS operates on two underlaying principles which seem to have an impact on social interactions and interpersonal relations including perception of others, social gregariousness, conformity, sexual conduct, or xenophobia among individuals, and populations. Several examples of the implications are discussed below.

One of the two principles is the 'Smoke Detector Principle'. As formerly mentioned, BIS does not respond to the "actual" presence of pathogens, but only to perceptual cues related to pathogens indicated by the senses. These perceptual cues might and might not predict the real presence of parasites and for that reason it works with error management theory. According to this theory, BIS should be set in favor of low-energy demanding errors. Often, the analogy of smoke detector is used (hence the name). The detector is sensitively set to evaluate any minor indication of potential danger as alarming and avoid later costs associated with actual fire. As a result, many false positive errors occur – individuals are marked as sick even when healthy. However, high sensitivity results in a low number of false negative errors. Incorrectly marking someone as healthy when sick increases the potential of getting infected. That is energetically costly as the individual uses tools of physiological immune system to combat pathogens, it increases the chance of becoming disabled or could lead to death. Hence, similarly to the smoke detector, BIS has evolved to be highly sensitive towards any signs of sickness, regardless of its severity. As a result, the processes involved in BIS might get activated even when the perceptual cues pose no actual risks (Nesse, 2005).

In addition, BIS also works on functional flexibility principle that is defined by stronger aversive reactions towards cues pertaining risk in situation when the individual is more threatened by an infection, or simply has a subjective feeling of an infection threat. However, with mild reactions in contexts the perceiver feels relatively invulnerable to pathogen infection (Miller & Maner, 2012). To illustrate, pregnant women, whose PIS is naturally suppressed tend to show negative attitudes towards outgroup members, possibly explained by their heightened vulnerability to pathogens (Navarrete et al., 2007).

Although, the principles might be beneficial for the individual/population, as the risk of getting infected decreases, the over-generalization does influence social interactions. Consequently, even entities with characteristics that share certain qualities with infectious stimuli tend to be judged rather negatively and possibly avoided.

4.5.1 Attention to Anomalies

To illustrate, people presented with chocolate fudge shaped into dog feces, or rubber vomit imitations responded with disgust and behavioral avoidance (Rozin et al., 1986). Similarly, it leads to negative attitudes towards humans who physically appear to be infectious, or to "deviate from the norm". Additionally, even people who simply show signs of exhaustion and present similar characteristics as the ill could be rated negatively. In a study based on visual cues, participants avoided handling props which had been previously touched by confederate with a birthmark on their face, despite the fact no risk of contagion could occur. The results were similar when compared to props touched by influenza infected confederate where the risk of contagion was actually present, showing an implicit bias of disease association with facial disfigurement (Ryan et al., 2012).

It could only be speculated whether non-threatening, but perhaps anomalous olfactory cues would induce similar behavioral reaction, as it has not been tested. Various body odors of non-contagious metabolic disorders were introduced in Chapter 3. For example, the sweat odor of patients suffering from phenylketonuria was reported to have a strange musty odor and the odor of patients with isovaleric acidemia was described as acrid, "cheesy" and "sweaty". Both odors were described rather negatively which could analogously to non-contagious visual cues induce avoidance behavior, despite no risks of infection.

4.5.2 Social Stigma and Prejudice

Additionally, even people without any morphological disfigurements, disabilities, or anomalies, but subjectively perceived as foreign are often stereotypically associated to pose as a threat (Markel & Stern, 2002). The reasons include a possible different physical appearance, perceived association of foreign people with foreign parasites, and different behavioral norms regarding to hygiene, or food preparation. In those cases, the perceived risk of getting infected strengthens and ethnocentric and xenophobic responses may occur. Even though it could be culturally specific, as in the region of Central Europe foreigners would not probably be treated as threats of infections - at least not verbally. Still, in general the different norms of hygiene, food preparation difference might be viewed as risky and increasing the chance of transmitting an infection.

Moreover, foreigners are often described to emit an unpleasant smell. Partly, it could stem from unfounded stereotypes, but it could be the result of different genetic make-up as well. It was illustrated in Chapter 2 that ethnicity (because of its genetic component) is one of the factors that helps to shape the overall body odor profile. To demonstrate, people of Asian origin were described to possess virtually no body odors due to the specific ABCC11 gene mutation and would rate the odor of other ethnicities as more prominent. Whilst individuals of African origin produce more intensive body odor, partly due to their higher amount and concentration of apocrine sweat glands (Martin et al., 2010; Prokop-Prigge et al., 2016). Similarly, diet influences human body odor too. Hence, the consumption of certain foods might account for some differences among populations. Traditionally, cultures of the East tend to have diets based on grains and vegetable with limited amount of meat products compared to consumers in the West (although it is increasing) (Nam et al., 2010). As mentioned, meat consumption could influence body odor and could result in certain differences. Nonetheless, the need to be cautious and not make controversial conclusions is necessary, as qualitatively all groups seem to produce the same volatile acid profiles (Prokop-Prigge et al., 2016). In general, cultural differences in ratings of certain odors appear, as a difference in ratings of odor pleasantness and edibility between Japanese and German participants occurred (Ayabe-Kanamura et al., 1998).

As already mentioned, in line with the functional flexibility principle, pregnant women from the United States in their first trimester showed attraction towards their ingroup and negativity towards outgroup members compared to later phases of pregnancy, possibly explained by their heightened vulnerability to pathogens (Navarrete et al., 2007). In another study, undergraduate students at University of British Columbia primed by visual cues of diseases, favored familiar immigrants compared to subjectively assessed foreign immigrants. In the same study it was shown that individuals' perceived vulnerability to disease (one´s personal belief about susceptibility to infectious diseases) impacts their attitudes towards others. Therefore, it was indicated that chronic and contextually evoked feelings of vulnerability towards diseases belong to the list of factors that add up to xenophobic tendencies (Faulkner et al., 2004).

4.5.3 Sexual Attitudes

Close interpersonal contact that comes with sexual activities increases the risk of disease transmission. However, the activation of BIS might lead to cautiousness in sexual relations. One of the examples was described above, when the odor of human feces activated BIS and increased the self-reported tendencies to use a condom (Tybur et al., 2011). In addition, in a set of studies, women (especially women who felt greater threat of getting infected) who anticipated a long-term future characterized by increased threats of diverse illnesses, would desire a greater variety in their future sexual partners. Women could desire sexual variety to increase genetic variability in their offspring, hence increasing the chance of survival of more individuals, as at least one could have immune genes necessary to survive (Hill et al., 2015). Although, it could be argued that higher number of sexual partners could increase the risk of getting infected throughout their own lives, it could be beneficial for the long-term future.

4.5.4 Social Gregariousness

Even non-sexual relationships present a certain risk of infections. Socially gregarious individuals tend to meet a great number of people and are likely to be more receptive to disease transmission (Nettle, 2005). Thus, the activation of BIS is thought to inhibit social interactions. In an experimental design, participants who were presented with disease salient visual stimuli reported lower levels of extraversion, with stronger avoidant motor movements in response to others (Mortensen et al., 2010). The experiment did not include control conditions of other threatening stimuli which means that the effects on social interactions might not be unique to threats posed only by infectious diseases. Despite the fact, the activation of

BIS seems to cause people to limit their social contacts and their heightened tendency to specifically choose those they prefer to contact.

4.5.5 Personal Attitudes

Those who subjectively felt more vulnerable to infectious diseases even had a stronger tendency to adhere to conformist statements and behaviors and the conditions of disease threat revealed higher conformist attitudes compared to the control group (Murray & Schaller, 2012).

In case that others violate social norms, people who chronically experience disgust more judge the "offenders" more harshly (Jones & Fitness, 2008). Participants exposed to a disgusting smell of a flatus spray tended to make more severe moral judgements on provided statements (Schnall et al., 2008).

Activation of BIS could even affect political affiliation, as people tend to be more conservative in disease salient situations, especially those who are more prone to disgust (Brenner & Inbar, 2015). Even political liberals exposed to a smell of disgusting odorant showed more negative attitudes towards homosexual men than to heterosexual men, compared to the control group where both groups were judged equally positively (Inbar et al., 2012).

Possibly, it could be argued that unpleasant odors of diseases would have similar effect on moral judgements and political affiliations of tested participants, but no such experiment has been conducted yet.

No research studying the effect of human body odors of people suffering from a disease/illness on the behavior of others has been conducted. However, the tendency to hedonically rate disease-related odors as more unpleasant, more intense, and unhealthier emerged. Furthermore, olfactory cues can play a role in the activation of BIS which can lead to avoidance behavior or have other effects on social phenomena such as xenophobia, social distancing, conformity, or political conservativism. Hence, it could be speculated that the odors of illnesses/diseases could activate BIS and navigate similar behavioral tendencies as explored for example through visual modality.

5. Diagnostics

The detection of disease-related olfactory cues might activate the mechanisms of BIS, induce disgust, and possibly lead to avoidance response, or to increase conformity to social norms, xenophobia, or ethnocentrism which should serve as ways to decrease the chance of pathogen exposure and subsequent infection. However, as formerly mentioned, BIS includes cognitive processes that allow people to empathize with those who are suffering from an illness or are disabled and allows to employ other strategies than avoidance behavior (Dongen, 2001; Jackson & Griffiths, 2014; Pryor et al., 2004). One of the possible outcomes of smelling a disease might be a correct diagnosis and subsequent choice of appropriate treatment. Hence, olfactory disease-related cues have a major potential to serve as early markers of ongoing issues, and odors could be used in simple non-invasive diagnostic tests.

As briefly outlined in Chapter 3, throughout history, various human body odors were used as markers for disease diagnostics. For example, Hippocrates, Galen, and Avicenna associated specific odors of urine, breath, or sputum with certain diseases. In modern times, diagnostics based on body odor cues has been rather underestimated, but it turns out body odors and further VOCs analysis of people suffering from a disease might have a potential. Furthermore, as it has been demonstrated by previously mentioned case studies, some medical professionals seem to come back to diagnostics based on olfactory cues (Centerwall & Centerwall, 2000; Hayden, 1980; Smith & Strang, 1958).

Famously, canines are considered magnificent smellers and have been trained to detect an odor of a specific disease in multiple cases. In addition, even other animals like mosquitoes, rats or mice might be trained to differentiate the odors of sick and healthy individuals. Although people are not commonly considered to be as great smellers as dogs are, they are able to smell many odors and their olfaction is excellent (McGann, 2017). The odors of diseases are no exception, as people can detect those too (Centerwall & Centerwall, 2000; Hayden, 1980; Sarolidou et al., 2020b). Especially hyperosmic individuals seem to have above average skills in detecting the smell of diseases. Additionally, powerful technological tools such as gas chromatography (GC), gas chromatography and mass spectrometry (GC-MS), or electronic noses are being used to identify disease-related VOCs (Kolk et al., 2010; Thriumani et al., 2018).

5.1 Diagnostics by Animals

With dogs' extraordinary capacity to detect and discriminate a major specter of odors, even at very minute concentrations, for long they have been used in various fields including law enforcement, in search and rescue teams, or military. They even turned out to be of help in the medical field and diagnostics, as it is possible to train them to discriminate between sick and healthy odors. Throughout the thesis, several examples of studies featuring dogs identifying diseases based on body odors have been introduced. Mostly, trained dogs are used to smell samples of various types of cancers. They could distinguish between samples of ovarian, bladder, lung cancers and healthy tissues, possibly suggesting a carcinoma-specific odor with a VOCs profile (Ehmann et al., 2012; Horvath et al., 2008, 2010; Willis et al., 2004). To illustrate on an example, Labradors could correctly identify patients suffering from colorectal cancer based on watery-stool samples with correct statistical significance, the tests were performed multiple times and confounding variables like smoking, other colorectal or inflammatory diseases did not affect the results (Sonoda et al., 2011).

Not only can dogs detect odors related to cancer, but they also seem to be capable of detecting infectious diseases. They turned out to detect the smell of bacteria *Clostridium difficile* (causing bowel infection causing diarrhea) from stool samples (Bomers et al., 2012, 2014; Bryce et al., 2017), infectious bacteria causing urinary tract infections (Maurer et al., 2016), and possibly to detect metabolic changes due to viral infections as in the case of bovine viral diarrhea virus, or coronavirus SARS-CoV-2 (Angle et al., 2016; Grandjean et al., pre-print). It was amidst the world pandemic of coronavirus disease SARS-CoV-2 that dogs were employed to detect the smell of infected patients. Although it was in studies which have not yet been peer-reviewed, the preliminary results show that dogs could detect the odor on pieces of clothing worn by infected individuals who were asymptomatic, or only had mild symptoms with high accuracy similar to RT-PCR tests and in a faster manner – they could do it within seconds, showing another evidence suggesting dog's impeccable ability to diagnose an illness based on odors (Grandjean et al., pre-print; Guest et al., pre-print; Jendrny et al., preprint).

Furthermore, foot odors of young children suffering from malaria presented to two trained dogs and they managed to distinguish the odors with mean sensitivity of more than 80% (Guest et al., 2019). When combined with the results from the study described in Chapter 3 showing that mosquitos are more attracted to the individuals that are infected with malaria, it seems that malaria too alters human body odor and could be diagnosed with the help of olfaction (Busula et al., 2017; Lacroix et al., 2005; Robinson et al., 2018). Interestingly, dogs even showed a responsive behavior towards samples of odors from patients suffering from epileptic seizures and discriminate them from their non-seizure states (Catala et al., 2019), or a tendency in detecting patient of narcolepsy (Dominguez-Ortega et al., 2013).

Dogs seem to perform correct diagnostics in many cases with sensitivity and specificity higher than chance. With their help specific VOCs related to illnesses could be identified to solve their biological profile. However, it must be noted that different breeds of dogs, approaches used in training and in administering the samples have been used. Various breeds of dogs vary in their smelling ability, it even depends on an individual dog within the breed. Some studies themselves remark that sometimes it is unclear whether the dogs could sniff out specific VOCs related to cancer, or other disease-related processes – like inflammation. Theoretically, VOCs produced by tumors that dogs can detect might be products of MHC genes mainly due to two reasons. As introduced in Chapter 2, MHC (HLA in humans) potentially influences human body odor. In addition, changes in HLA seem to have an association with cancer. Tumor transformation is often associated with low molecules expression of classical HLA class I, suggesting a relation between the two (Balseiro & Correia, 2006).

Nonetheless, dogs, or mosquitoes are not the only animals capable to smell an illness. Even though they are not necessarily traditionally used in diagnostics per se and do not seem to show a spontaneous preference for diseased individuals, it is possible to train mice to discriminate odors of for example cancerous patients (Kokocinska et al., 2020; Sato et al., 2017). Moreover, rats could even detect odors of infectious tuberculosis when presented with sputum samples (Kanaan et al., 2021; Mulder et al., 2017; Reither et al., 2015).

Even though animal studies are promising and show potential in the field of diagnosing diseases using human body odor, they do have some drawbacks. Animal trainings are lengthy, expensive, could lead to exhaustion and animals cannot report on their used strategy and be involved in day-to-day diagnostics. Animals' behavior can be potentially unpredictable, vulnerable to distractions and other stimuli in the environment limiting their use outside laboratory when not reflected upon (Hackner & Pleil, 2017). Moreover, in case of infectious diseases, dogs could have the risk of possible infection from the pathogens, hence should be tested regularly.

Nevertheless, animal smelling skills are priceless and could help in the process of developing highly functioning technologies using molecular analysis with great precision.

5.2 Diagnostics by Humans

Even though it is often overlooked, people too can smell the odors of diseases. As previously mentioned, multiple times several diseases were associated with different types of odors (Centerwall & Centerwall, 2000; Hayden, 1980; Smith & Strang, 1958). Possibly, all people can use their sense of smell more and use it for diagnostic purposes when one's smell somehow differs. However, in the process of diagnostics, hyperosmic individuals with above-average smelling skills might be useful in the creation of advanced tools in medical practice.

In Chapter 3, a hyperosmic woman who could smell the odor of Parkinson's disease (PD) was introduced. Firstly, she noticed a peculiar smell emanating from her husband, but years later recognized that all PD patients had a nasty musky scent of different intensity. The characteristic odor was displeasing to Milne, she argued with her husband to shower more, but it did not help. Additionally, the odor had a lasting effect on bed sheets and clothing and was difficult to wash it off. Although she considered the odor unpleasant, and her BIS could have potentially activated as she employed different strategies to get rid of the unpleasant smell - she decided to contact PD-involved researchers to elaborate. At first, her observations were dismissed, however a pilot study with 12 individuals involving 6 PD patients and 6 controls showed her success rate to be 100%. She even identified 1 patient from the control group who was diagnosed months later (Morgan, 2016). After the case had been covered in media, several other people reported they could distinguish the specific smell of PD, and other diseases supporting the trend.

Currently no blood and laboratory tests to diagnose non-genetic PD exist, and no known cure exists. PD is diagnosed by neurologists mainly based on occurrence of symptoms of shaking, balance issues, slowness. In addition, these signs often appear in advanced stages of the disease and may co-occur with other diseases as well and patients might be misdiagnosed. The symptoms might be relieved by medicine, surgery, or other therapy, but the earlier it is diagnosed, the more effective the course of the disease might be. For that reason, Milne's abilities brought enthusiasm to researchers in various fields. Her ability to correctly identify specific VOCs related to PD (or even other diseases), could potentially lead to a development of a commercially used diagnostic tool to detect PD in its early stages, before any other signs appear. The odor was mostly related to sebum on the upper back; hence any further analyses primarily focus on it. A study which aimed to discover biomarkers of PD present in sebum, found 10 compounds associated with PD patients using spectrometry methods (Sinclair et al., 2021). Similar and promising results were replicated in another study as well by using a simple, non-invasive skin swab of sebum on their backs Sinclair et. al (2021). Based on current research, the goal is to create a non-invasive, inexpensive, widespread commercially used test to analyze the odor of the sebum of an individual and provide reliable results. Possibly, Milne's sense of smell, or the abilities of other hyperosmic people might be used in identifying VOCs in other diseases. Based on her personal reports tuberculosis smells like wet cardboard and brine, Alzheimer's disease like musky vanilla, liver disease smells fecal, and cancer allegedly has an "earthy smell".

5.3 Diagnostics by Analysis of Volatile Organic Compounds

The idea to use human body odors and analyze VOCs emanating from skin, breath, or urine is highly valued, because it is a non-invasive and quite promising method of diagnosing various illnesses and diseases in their early stages even in cases when other diagnostic techniques fail. It motivates a development of odor detection instruments which work unambiguously, with high reliability and validity of detection and analysis of VOCs at highly accurate levels.

Hence, various advanced technologies like GC, GC-MS, or electronic noses emerged which can identify illness-specific biomarkers. Above, these technologies have been shown to be used in the analysis of the smell of cancer, Parkinson's disease, cholera, tuberculosis, or other diseases in VOCs analysis. Technologies based on GC firstly separate the complex VOCs mixture into individual compounds and thereafter analyze them in a sequence using a detector. The detector could be a gas sensor, MS system, or ion mobility spectrometry. These tools are highly sensitive and effective, but typically do not operate in real time and are not viable for quick analysis that could be performed at home, or even at the doctor's office. Therefore, smaller sensor systems have been in development to detect various odors. Portable GC-MS technologies have been introduced to address the issue and reduce the runtime, but the results are less accurate (Poirier et al., 2021). In addition, electronic noses (e-noses) belong to one of these real time technologies and represent a device that should enable to identify and discriminate between diseases. These devices should be able to analyze exhaled breath, VOCs in urine, blood, or sweat – all reported in Chapter 1 as important sources of human body odor. In e-noses, VOCs are presented to a sampling interface and encounter a gas sensor, consequently a response is transmitted to a computer which tries to recognize a pattern. However, all e-noses do need further research to perfect them and utilize it in commercial environment, mainly due to incomplete VOCs profiles of most diseases.

To illustrate, when two types of e-noses were tested to analyze the sputum samples of individuals with tuberculosis, the results showed them to be insufficient in differentiating the samples necessary at diagnostic levels (Kolk et al., 2010). In the case of melanoma patients, VOCs emitted by skin lesions analyzed by e-nose showed accuracy of around 80% which was similar to more time-consuming diagnostic methods at the time (D'amico et al., 2008). Examining urine samples of 15 subjects with diabetes type II. with the help of e-nose technology distinguished them from the control with a success rate of 97%, although promising, it must be taken with caution as most of the devices are in their prototype stages and far from the state when they can be used as reliable commercial products (Arasaradnam et al., 2011).

All studies have in common that they call for more research in their fields and specific VOCs profile of different diseases and illnesses are needed to fully use the potential of the devices. Potentially, hyperosmic individuals could collaborate and help in the identification of VOCs as Milne did in case of PD. In her case, the research team separated individual VOCs and let her smell it and mark which ones make up the odor profile of the disease.

The odors related to illnesses and diseases could activate BIS and perhaps avoidance behavior mechanisms in order not to get infected. Nevertheless, in society people have the ability to cognitively evaluate the situation and act pro-socially, even in cases it could impair their health. It manifests itself in diagnostics, when individuals' symptoms are analyzed and consequently treated, if possible.

In current medicine, olfaction is rarely used, as usually more advanced diagnostics tools are available. However, it was demonstrated that VOCs emanating from disease-affected individuals might be of great importance in early and non-invasive diagnostics when other methods fail. Analysis of VOCs could potentially be cheaper, easier to operate, and testing could be performed on a regular basis, often detecting diseases in their early stages. With the help of dogs, or hyperosmic people, more advanced technological tools are created and show great potential in previously unexplored areas.

6. Discussion

According to various studies indicated above, some illnesses/diseases do have an impact on human body odor, affect it in a way that can be detected by others and potentially induce a behavioral response. Infectious diseases, metabolic, psychiatric disorders and neurological disorders, or even poising may impact human odors and are often characterized by foul, intensive, musty and musky smells, others have sweet and sugary odors. (Bondy et al., 1980; Menkes, 1959).

It was shown that disease-related cues could play a role in the behavioral immune system. In theory, the odors of ill conspecifics should be unpleasant, induce disgust (the main emotion in BIS) resulting in avoidance behavior ensuring not contracting an illness. Currently, a tendency appears for participants to hedonically rate the illness-related odors as more intensive and less pleasant. The odors of illnesses may induce neurological changes even at unconscious levels when no conscious hedonic negative rating occurs, and it should be explored further. However, it has not yet been studied if disgust was experienced by the affected.

This might very well work in case of some diseases that alter the body odor in a way which is considered unpleasant, but what about the cases when more pleasant odors are emanated that are similar to freshly baked bread, maple syrup, or sugary donut? Moreover, not all diseases are infectious, why would people avoid those that suffer with metabolic disorders, cancers, or toxin poisoning?

Not all diseases alter human body odor, although this needs further testing. In that case, it might be speculated why some diseases emanate a smell, whilst others not, or why can people detect only some if it should help them in avoiding getting ill. It is likely that disease-related odors are solely by-products of metabolic processes that occur when body goes through an illness. As explained earlier, in short, body odor is a result of bacteria and microorganisms breaking down sweat. In some illnesses, the pathogen alters the levels and types of those microbes which could adjust the odor. Also, activated immune system changes the excretion of certain metabolic products also changing the body chemistry. In that case, disease-related odors might not be an adaptive mechanism and play a specific role in disease avoidance whatsoever.

In addition, some disease-related smells are described as pungent and disgusting, others as sweet, cinnamon and bread like. Possibly, with the unpleasant smells of infectious diseases, people could have developed perceptual mechanisms that helped them to distinguish them better and avoid them. In most humans, the pleasant smells will probably not produce an emotion of disgust and avoidance behavior. The question then is, why some diseases could have the power to induce disgust, or at least are rated as unpleasant and off-putting, whilst other might be considered pleasant. When considering the odor of malaria, we could note that the malaria causing pathogen in line with the proposed manipulation theory alters the body odor in a way that is pleasant and attracts mosquitoes which helps the pathogens to spread more. It could benefit people to distinguish all diseases as unpleasant, or benefit pathogens to all smell nicely in order not to get avoided or be attracted by carriers and increasing their chance of transmission.

Not all illnesses are contagious – metabolic, genetic, psychiatric, or neurodegenerative disorders cannot be transmitted through direct contact and avoidance behavior is counterproductive. It could be speculated that people do not choose those individuals as partners in order to reproduce with them and pass on the same genes. Nonetheless, it was demonstrated that in line with overgeneralizing mechanisms of BIS, only superficial cues potentially indicating a disease are analyzed and people avoid those who pose no risk of infection, even if they are cognitively aware of it. Even psychiatric diseases like Schizophrenia which has been mentioned above to alter human odor develop earlier in life, or at least tends to be diagnosed in 20s and 30s (Gogtay et al., 2011). Hence, the partner selection theory could be valid for heterosexual couples in many metabolic, genetic, or psychiatric diseases that develop early in life. However, according to statistical data cancers, or neurodegenerative diseases often appear late in age when individuals are no longer in their reproductive phase. In case of cancer, approximately 70% of cancer cases occur in those aged over 50 (Roser & Ritchie, 2015). The prevalence of neurogenerative diseases also increases with higher age (Hou et al., 2019). Although, undoubtedly, those could also appear earlier in younger people as well, especially the trend is rising nowadays (Miller et al., 2020).

In case of poisoning, which is also not contagious, it might be beneficial to avoid those who employ risky behavior that got them poisoned in the first place and to avoid the environments in which the people occur and could have potentially been poisoned.

Even though, disease-related odors could very well play an important role in BIS and serve as cues to avoid pathogens and save the body's energy which would be instead used by PIS to defend the body, it is quite difficult to make sweeping generalizations. Unfortunately, no study has directly researched whether the odors of diseases elicit disgust. The fact that people tend to rate the odors as less pleasant and more intensive does not imply it elicits disgust, or that avoidance behavior would be employed. Future studies could employ more measuring techniques at once, the respondents could fill out standardized self-reporting questionnaires, neural activity could be scanned, facial electromyography would measure the activity of facial expressions and behavioral observance might be involved too. The integrated approach could clarify, or at least look closer at the mechanisms that follow detecting (whether consciously/unconsciously) an odor-related to illnesses and propose whether disgust ensues. Furthermore, the behavioral outcome which might follow has not been studied either and could be an interesting contribution to the field.

In general, the research is in its beginnings, but progressively it could be tested how different diseases are rated. Potentially, infectious, metabolic, or psychiatric diseases could induce different reactions. Some could be rated as pleasant, some unpleasant, or not hedonically detectable at all. In addition, it would be interesting whether some odors of diseases are only processed unconsciously and show some brain activity, whilst no self-reported change occurs, as has been already recorded by some studies (Regenbogen et al., 2017). Additionally, in line with research of de Groot et al. (2012) when it seems that the odor of disgust and fear is transmitted from the communicator to the receiver (emotional contagion), it could be studied if people exposed to odors of diseases also exhibit any activation of their PIS and whether their own body odor changes.

As mentioned in the previous chapters, some studies have been conducted to test people's reaction to the scent of illnesses, but mostly by using endotoxin LPS to artificially induce inflammatory processes (Olsson et al., 2014; Regenbogen et al., 2017; Sarolidou et al., 2020b). The approach has often been criticized even by the researchers themselves calling for more experiments done with natural sickness model. Although it was once conducted with a respiratory infection, the sample was small and the patients had only mild symptoms which could have not had an impact on the body odor and it has not been replicated since (Sarolidou, et al., 2020b). Though, the approach is logistically demanding, and it is difficult to obtain multiple samples from patients suffering from an illness that meets the requirements. Also, it needs to be done with caution, as working with infectious diseases could endanger involved parties.

Moreover, the data on disease-related odors usually come from individual case studies, doctor's testimonies, or "common knowledge" (Centerwall & Centerwall, 2000; Hayden, 1980; Smith & Strang, 1958). Therefore, it might be beneficial to test people's hedonic ratings of odors affected by diseases, both infectious, metabolic, or psychiatric more systematically. It could show whether the odors are consciously detectable, but also how they are rated in terms of intensity, or pleasantness.

Nonetheless, chemical assays and volatile compounds analyses have been performed to pinpoint specific volatiles related to some diseases. That could very much help in creating diagnostics tools like e-noses which would be used as non-invasive, inexpensive tools that could perform routine diagnostics. The development process is quite arduous and lengthy. It is still necessary to compose full VOCs profiles of various disease which could reliably predict its occurrence. The size and price of the technology is currently also an issue, as the most precise GC-MS analyzing tools are quite spacious and expensive. Smaller technologies are less exact and commercially available for regular usage. However, it is only a matter of time, resources that the promising field will emerge, and certain diseases will be diagnosed via non-invasive VOCs analysis.

It has been demonstrated that each person has a unique body odor which is partly genetically determined but could be changed by diseases and illnesses. However, it must be mentioned, it is difficult to disentangle genetic and environmental factors contributing to body odor and hence to study the odor of a disease removed from other influences. The resulting body odor is always a combination of multiple factors which must be considered. For example, the body odor of an ill individual might be altered even due to the change of his/her hygienic practices, diet, liquid intake, medicine intake, induce of extensive sweating and even his/her mood. The researchers know confounding variables might have a possible impact, and try to keep them stable, or reduce them. For example, the subjects are asked to exclude certain foods from their diet, and in case of collecting samples of axillary odor, use non-perfumed cosmetic and hygienic products, abstain from sexual contact, or are asked to sleep alone in their bed (the samples are often collected at night whilst the subjects are wearing a t-shirt with underarm pads) in the timeframe of the experiment. On the other hand, the laboratory conditions impact the ecological validity, as in real life it is not as strict and separable.

Additionally, even obtaining human body odor samples is not as straight-forward. In general, many studies regarding human body odors work mainly with samples from the axillae. Since they are richly covered with apocrine glands and bacteria, they are believed to give rise to the specific body odor. Also, the sample collection from the axillae is quite easy and straightforward. Despite that, other sources cannot be ignored. Even though, research covering the body odors of diseases also often includes urine or breath odor samples, other body sources are mostly omitted. So far, it is unclear whether and how body odors from different sources are related, but in a recent experiment it was demonstrated that in adult women and infants - axillary, breast, and head odors are informative and lead to recognition of the odor (Hierl et al., 2021; Poirier et al., 2021). Based on research done with the Parkinson's disease, it was demonstrated that even less expected places such as the upper back could inform about diseases with greater precision than axillary odor (Sinclair et al., 2021). Or in case of lung cancer, the odor of one's breath would be considered more essential. It serves as an example to consider paying attention to multiple body odor sources in future experiments, as different body parts can inform about various diseases more precisely.

One of the challenges that also needs to be addressed is related to tested populations. In general, psychological research is mostly done in western, educated, industrialized, rich and democratic countries (WEIRD), with odor related studies not being an exception. In case of research on olfaction, current studies cover rather old, deodorized, and desensitized (ODD) populations which mostly overlap with WEIRD countries. More specifically, it means that the studies are performed on Euro-American adult student populations, often excluding children, seniors, and non-Euro-American populations. However, human body odor perception, but even emanation might be quite culturally specific due to ethnicity, or dietary factors. For instance, when the odor detection skills of native Amazonian tribe of Tsimane' were compared to industrialized Germans, it turned out that Tsimane' population could detect n-butanol solutions at lower concentrations showing their better skills of odor detection (Sorokowska et al., 2013). The explanation might be cultural, environmental, genetic, or their combination, but the important fact is that a difference emerged between a WEIRD/ODD and non-WEIRD/non-ODD population. It might be speculated that non-industrialized populations are better at using their sense of smell and would be better at identifying the odors of diseases and avoid them more often, as it would compensate for the lack of other diagnostic tools, or medicine. Possibly, these populations may have a more sensitive sense of smell, or they are simply better at it since they are more in touch with their natural scent and use their sense on a regular basis and it is only a question of repeated training. In case of a native tribe Onge of Andaman Islands they think in smells and define everything primarily by smell, it is a population that has a culture and a language rich in odors and it is part of their identity (Fox, 1999). It could be priceless to see their perception of odors related to diseases. Also, it could show that learning is a part of the process of using the sense of smell well, as it is integrated into every aspect of their life. In that case, similarly, other cultures could become more odor-sensitive if it was their conscious objective.

But odor emanation is specific as well. One of the factors is ethnicity. As already outlined in Chapter 2, most people of Asian descent have a specific mutation of the ABCC11 gene which results in a weaker axillary odor compared to those of African, or European descent (Martin et al., 2010). Moreover, another article states that axillary odors vary quantitatively based on ethnicity, but no qualitative differences were observed, adding that other biochemical pathways are involved in addition to ABCC11 (Prokop-Prigge et al., 2016). As a result, it could even have an impact on disease-related odors and their perception and emanation. The studies should cover various cultures and ethnicities to control for its possible impact. Also, it was previously mentioned that diet might be culture-specific too (more meat consumption in western regions) and it could impact the resulting odor, when combined with a certain disease, the profile could be different. Regarding cross-cultural studies of disease-related illnesses, it could be studied if the ratings and reactions of different diseases had been the same, or a different response would follow.

Most studies in olfaction are mainly performed in relation to mate choice and sexual selection. Mostly women are the raters of odor samples provided by men, since women are considered as the ones choosing their partner, also as better smellers putting greater emphasis on odors (Havlicek et al., 2005). However, it is not as straight-forward to claim that mate choice is strictly one-sided, as men choose their partners too. In addition, it usually excludes non-heterosexual couples where communication based on odors might play a role. Nonetheless, it is beneficial for both males and females, regardless of their orientation to avoid pathogen exposure in case of social interactions with infected conspecifics, not only in cases of mate and sexual selection. Hence, it could be studied more universally – both women and men should rate and donate their body odors related to illnesses and diseases.

This thesis itself needs to be reflected as well. It presented a bigger picture of the role of disease-related odors, put it into context of the behavioral immune system and outlined possible social consequences. In addition, it showed a great potential of VOCs analysis and odor recognition of diseases and the benefit it could bring into diagnostics which could be timely, cheaper, non-invasive, and occurring at a regular basis. However, as it covered a rich spectrum of complex topics, some concepts were shortened, or discussed briefly.

Conclusion

The main aim of this thesis was to critically review and evaluate current scientific research within the field of human body odors, illnesses/diseases, and behavioral immune system by conducting a thorough literature analysis.

It seems that some infectious illnesses, metabolic and genetic disorders, but even psychiatric disorders and poisoning affect body odor, but even urine and breath odor.

Importantly for the scope of this thesis, the question was whether disease-related olfactory cues can affect the behavior of other conspecifics. It seems that olfactory cues can play a role in behavioral immune system (BIS) which was proposed to exist as a set of psychological mechanisms to avoid pathogen exposure and consequent activation of costly physiological immune system (PIS). Based on several studies, body odors of donors injected with endotoxin LPS causing an immunological response mimicking a real-life infection, were rated as less pleasant and more intensive (Gordon et al., 2018; Olsson et al., 2014; Sarolidou et al., 2020b). Even a slight tendency to rate the odors of patients with respiratory disease as less pleasant emerged (Sarolidou et al., 2020b).

Therefore, it could be assumed that BIS would be activated based on perception of olfactory cues related to an illness which would thereafter start a process of affective mechanisms inducing disgust in the individual and cognitive mechanisms evaluating the risk of the situation which could all consequently lead to a behavioral response – avoidance behavior. As a result, the individual would avoid his/her pathogen exposure and save the body's energy, otherwise needed for PIS to operate.

Nonetheless, the activation of BIS might not be without its cost as well. As pathogens are undetectable by themselves, and BIS must operate based on superficial cues, sometimes mistakes are made, and BIS could activate towards people that do not pose as risk at all. Activation of BIS can influence multiple social situations. It affects sexual attitudes, social gregariousness, and even own moral, personal and political opinions and as a result people tend to become more conservative, restricted, cautious, and even more hateful. Repeatedly, it must be underlined, that currently, no research has been performed to test whether disease/illness-related olfactory cues induce avoidance behavior and activate BIS, hence one must be careful when drawing any conclusion.

The smell of diseases might possibly lead to hostile or avoidant attitudes towards those who emanate it. At the same time, analysis and detection of volatile organic compounds related to numerous diseases might lead to prosocial behavior as well. Hence, the thesis covered diagnostics that could be performed by animals like dogs with great sniffing abilities, but even by hyperosmic individuals who with the help of experts could develop non-invasive, inexpensive tests to diagnose diseases in their early stages even when other methods fail. Many researchers work on electronic devices that could analyze VOCs particles emanating from different people and determining if they have an illness. However, still much work is required.

Researchers have come a long way in uncovering pieces of information about diseases impacting human body odor and the behavioral immune system. It seems that disease-related olfactory cues could be part of the behavioral immune system, but much is yet unknown. Even with all the unanswered questions and limitations, it is key to employ an interdisciplinary approach, combining knowledge from biology, social sciences, and technologies to understand the processes better.

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