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REVIEW

Olfactory Sensitivity in Mammalian Species

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Summary

Olfaction enables most mammalian species to detect and discriminate vast numbers of chemical structures called odorants and pheromones. The perception of such chemical compounds is mediated *via* two major olfactory systems, the main olfactory system and the vomeronasal system, as well as minor systems, such as the septal organ and the Grueneberg ganglion. Distinct differences exist not only among species but also among individuals in terms of their olfactory sensitivity; however, little is known about the mechanisms that determine these differences. In research on the olfactory sensitivity of mammals, scientists thus depend in most cases on behavioral testing. In this article, we reviewed scientific studies performed on various mammalian species using different methodologies and target chemical substances. Human and non-human primates as well as rodents and dogs are the most frequently studied species. Olfactory threshold studies on other species do not exist with the exception of domestic pigs. Olfactory testing performed on seals, elephants, and bats focused more on discriminative abilities than on sensitivity. An overview of olfactory sensitivity studies as well as olfactory detection ability in most studied mammalian species is presented here, focusing on comparable olfactory detection thresholds. The basics of olfactory perception and olfactory sensitivity factors are also described.

Key words

Olfaction • Sensitivity • Odor detection threshold • Mammals

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Introduction

Chemosensory systems develop very early in ontogeny and are found in almost every animal. The mammalian sense of smell detects and discriminates between innumerable substances that have very diverse chemical structures and features (Corcelli *et al.* 2010). The omnipresent chemical stimuli enable detection and discrimination of home range, conspecifics, mates, mother, food resources, predators, and prey. Chemosensation is critical for survival and reproductive success (Wilson 2006). Many species use chemical cues to recognize genetically related kin, even the identity of conspecifics using individual olfactory cues in order to avoid inbreeding as well as to determine the animal's reproductive status (Wilson 2006, Cometto-Muniz and Abraham 2008). Olfaction also helps protects the entire organism as this system provides an early warning system for the detection of health hazards and imminent threats (fire, leaking natural gas, rotten food, or toxins) and plays a critical role in nutrition (Laska and Hudson 1993, Hawkes and Doty 2009). The sensory and hedonic

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evaluations of most food-related flavors are mainly dependent on olfactory perception (Nevitt 2000).

Chemosensory-based communication is a vital signaling tool (Frasnelli *et al.* 2011). From the most gregarious to the most solitary, all animals need to coordinate their activities with others of the same species. This coordination is based on communication (Laberge and Hara 2004), which involves utilization of chemical signals known as pheromones (sexual attractant pheromones, mammary pheromones, aggression pheromones, alarm pheromones, marking pheromones) (Brennan 2010).

Olfactory sensitivity in mammals has been studied since the 1960s, but experiments focused on an exact olfactory threshold are rare. The small number of these experiments differs in methods as well as in results. The main aim of this review is to present the olfactory thresholds of mammalian species and to show the exclusivity of the olfactory system in mammals, despite the differences in the results of individual studies.

There has been a long-term effort to compare odor perception in humans and animals. The comparison may develop scientific evidence concerning hypotheses about relative olfactory powers in humans and other mammalian species. An important criterion is the integration of human psychophysical results with animal results in similar studies, as animal results may approximate the neural mechanism and olfactory perception in humans (Walker and Jennings 1991).

What is olfaction?

Olfaction mediates the perception of volatile chemicals, which convey information about the environment to the receiver. Variations in the precise structure of individual odorant molecules, concentrations of those molecules, and specific combinations and relative concentrations of components in a mixture of odorant molecules provide crucial information about the surrounding world. Given that most odors are complex mixtures of a number of single components, the discrimination of one odor from another is difficult, and previous experience enhances odor discrimination in mammalian species (Firestein 2001, Croy *et al.* 2015).

Over time, a number of theories have been attempted to explain the relationship between the molecular structure and odor in the primary olfactory reception mechanism. The view of the reception mechanism evolved from the "lock and key" theories that claim molecular shape determines odor (Wright 1977, Frater 1998) over odotope theory-based identification of receptor subtypes responding not to one but to many odorants (Mori 1994, Malnic *et al.* 1999) to vibration theory (Turin and Yoshii 2003). This theory, based on the molecular vibrations of odorants, was first described in 1938 (Dyson 1938) and has been newly extended by Turin (2002). This theory states that odor is determined by the vibration spectrum of the molecule. The detection mechanism is based on inelastic electron tunneling, and the vibration spectra of the odorants determine their odor (Turin and Yoshii 2003), but after clean chemical deuteration studies (Block *et al.* 2015) the vibration theory should be reexamined (Vosshal 2015). In conclusion, no theory explaining the principles of the odorant-receptor interaction has been proved to be entirely plausible (Zarzo 2007).

Individual variations in the limits of detection for different stimuli have been known for a long time. Although individual odor thresholds vary, studies have indicated the variations within an individual are comparable to variations between individuals (Cain 1989). The olfactory threshold is the minimum concentration of a target stimulus an individual is able to reliably differentiate from a blank sample (deionized water in most studies). In recent experiments that focused on olfactory sensitivity in mammalian species, the olfactory detection threshold (ODT) was considered the limit of olfactory sensitivity.

Olfactory subsystems

In mammals, the olfactory, gustatory, and trigeminal systems are involved in chemical senses (sense of smell, taste, somatosensation). The nose, the main olfactory organ, consists of multiple olfactory subsystems, among which the main olfactory epithelium (MOE) and the vomeronasal organ (VNO) have been the most studied (Trotier 2011). The MOE is composed of two types of cells, microvillar cells and olfactory sensory neurons (OSNs), which express G-protein-coupled odorant receptors. The VNO contains two olfactory subsystems (apical and basal) and two classes of vomeronasal receptors (V1Rs and V2Rs) (Young *et al.* 2010). Although human embryonic VNO exerts a developmental track common to microsmatic mammals, after the initial development, the VNO regresses, with only a few vestiges persisting in adults and most

chemoreceptor cells within the persistent vomeronasal duct (VND) wear off. By the absence of neurons and vomeronasal nerve bundles it can be deduced that the vomeronasal epithelium is not a sensory organ in adult humans (Trotier *et al.* 2000). The genes that code for the V1R-type and V2R-type receptor proteins are mostly nonfunctional in humans (Mohedano-Moriano *et al.* 2008). Although vomeronasal ducts and pits have been observed in humans (Moran *et al.* 1991, Stensaas *et al.* 1991, Boehm and Gasser 1993, Trotier and Doving 1996), evidence of functional vomeronasal receptor neurons connected to the brain has not been found in adult humans (Johnson 1998, Smith *et al.* 2014). In some species, there are two additional spatially segregated clusters of sensory cells, the septal organ (SO) (Storan and Key 2006) and the Grueneberg ganglion (GG), which are particularly well developed in mice (Brechbuhl *et al.* 2014). Each of the four physically segregated apparatuses can convey sensory information about multiple modalities and serve multiple functions. Although these chemosensory subsystems detect distinct chemical substances, the olfactory cues overlap substantially. No behavioral studies have tested the olfactory subsystems separately, since it is not possible to test only part of the complex olfactory system without an invasive intervention in the subject organism.

Main factors of olfactory sensitivity

An animal's sense of smell enables the animal to recognize and discriminate numerous airborne molecules with great accuracy and sensitivity (Wu *et al.* 2011). The behavioral relevance of an odorant may be an important determinant of a species' olfactory sensitivity (Laska *et al.* 2005a, 2007a, Olsson and Laska 2010, Ferdenzi *et al.* 2013). It has also been determined that olfactory acuity increases during fasting, allowing some mammalian species to detect food and environmental odors, such as those of predators, more easily (Aime *et al.* 2007). The connection between body weight and olfactory sensitivity has been observed in mammals, especially in rats (Thanos *et al.* 2013). Changes in olfactory sensitivity are related to circadian locomotor behavior as well. Odor stimuli can act as a circadian time cue that modulate circadian behavior in mammals (Abraham *et al.* 2013). To utilize chemical cues, animals must have olfactory systems that can deal with at least four specific issues: 1) the detection of the stimulus; 2) discrimination of the stimulus from other potentially very similar stimuli; 3) dealing with and, perhaps, determining relative stimulus intensity; and 4) assigning meaning to the stimulus (Wilson 2006, Wilson and Mainen 2006). Detection is the degree of presence, while recognition involves matching input, and identification is the assignment of meaning. These three different functions do not necessarily correlate with specific anatomical locations (Mombaerts 2001).

Repeated exposure is an important factor in developing olfactory sensitivity, so learning is evidently a vital part of olfactory perception (Wilson and Stevenson 2003). The synapses and receptive fields of the cerebral cortex are plastic. Modification of cortical inputs leads to synaptic changes, which are related to improved sensory perception and enhanced behavioral performance (Guthoff *et al.* 2009). Not only the olfactory threshold but also the olfactory discrimination of similar odorants (odor acuity) in general can improve with experience (Ferdenzi *et al.* 2013), and the ability to successfully distinguish between similar odorants depends on the specific behavioral response of particular species (Giannaris *et al.* 2002, Wiltrout *et al.* 2003). The role of experience was found even in the prenatal stage in the rabbit (Coureaud *et al.* 2004). Some studies suggested that repeated exposure to an odorant may influence the threshold level. The exposure to either amyl acetate or androstenone in mice leads to enhanced sensitivity (Yee and Wysocki 2001). Conversely, some investigations found that repeated or prolonged exposure to an odorant decreases olfactory sensitivity to that odorant; however, the sensitivity recovers over time in the absence of exposure (Hudson 1999). It seems to be dependent on the concentration of the odor as well as on the duration of exposure (Moberg *et al.* 1999). The detection threshold obtained before and after exposure also shows an adaptation effect that is characteristic of continuous exposure (Haehner *et al.* 2007, Hummel *et al.* 2007). The adaptation and desensitization of the olfactory response were thoroughly reviewed by Kleene (2008).

Some odorants smell qualitatively different at high concentrations. Higher concentrations of any odorant are likely to result in progressively more widespread binding to different types of receptors (Duchamp-Viret *et al.* 1990, Malnic 1999). Rabbit pups responded to the mammary pheromone only when it was presented within a fairly limited concentration range. Only a specific concentration leads to the behavioral response. This is consistent with the notion that higher concentrations actively recruit more receptors, thus

changing the quality of the receptor output (Coureaud *et al.* 2004). It has also been suggested that some olfactory sensitivity differences dependent on sex may exist in humans (Ferdenzi *et al.* 2013), non-human primates (Laska *et al.* 2007a), and dogs (Wells and Hepper 2003). Nucleotide polymorphisms and variations in genes that express olfactory receptors may be the proximate cause of differences between the sexes. Nevertheless, the behavioral relevance (attractiveness or deterrence) of an odorant may be the ultimate cause (Laska *et al.* 2007a). Some gender-based olfactory sensitivity differences were determined with the use of aromatic aldehyde bourgeonal (Olsson and Laska 2010, Ferdenzi *et al.* 2013), but it has also been shown that olfactory thresholds are extremely variable across subjects (Stevens *et al.* 1988) and change substantially over time in humans. This is also the case for shorter periods (Stevens and Dadarwala 1993).

Olfactory receptors in mammals are encoded by the largest gene family charted in the mammalian genome. High number of amino acid changes is affected by high level of polymorphism, high number of pseudogenes and many allelic variants (Quignon *et al.* 2005, Tacher *et al.* 2005). Moreover, the anatomical features of intranasal volumes and the nasal cavity were found to have an influence in dogs (Damm *et al.* 2002). It has been proven that olfactory sensitivity also changes during an animal's lifetime, and this also applies to certain mammalian species (Doty 1989, Wells and Hepper 2003).

It has been suggested that in mammals, such as dogs, that have a very acute sense of smell, an anatomical structure called the olfactory recess determines olfactory superiority in comparison with animals, such humans that lack this structure. It has been demonstrated in the fluid dynamics of canine olfaction that a unique nasal airflow pattern develops during sniffing, which is optimized for odorant transport to the olfactory part of the nose. Thus, mammalian olfactory function and acuity may depend on the transport of odorant molecules to the olfactory recess where the odorant receptors are exposed to prolonged contact with them (Craven *et al.* 2010, Sobel *et al.* 2000). One study, which indicated that apparent sensitivity to some odorants is significantly greater at high nasal flow rates while other odorants exhibit the opposite effect, showed this connection to be contradictory. When the airflow rate and sniffing frequency in mice were evaluated separately, the nasal airflow rate, instead of the sniffing frequency, was found to affect the observed response in the olfactory glomeruli (Oka *et al.* 2009).

In studies conducted on olfactory sensitivity in mammalian species, the experiments focus on the capability of the studied subject to detect the target substance or to distinguish between two or more different substances. In some studies on olfactory sensitivity, the capability to detect a target odorant is considered. The methodology of individual experiments differed in the searching and marking of the target substance as well as in the chemical nature and concentration of the target substance. In recent studies, behavioral tests were used mostly to determine the odor detection threshold. The ODT is determined by testing the animals' ability to discriminate between a target odor and a blind sample that comprises an odorless object. Behavioral tests are based on instrumental conditioning and multiple-choice tests. In multiple-choice tests, the subjects must find and distinctly mark the target substance in different concentrations and are rewarded with food for the correct answer. The descending staircase procedure is usually repeated, and to mix the exact concentration of the target odorant, an odorless solvent is used in the multiple-choice test with a blind sample.

When the concentration detection function is measured, an alternative forced-choice procedure against air as a blank sample and an ascending concentration of target odor are usually used in humans. ODTs were defined as the concentration producing detectability (P) halfway (P=0.5) between chance (P=0.0) and perfect detection (P=1.0). Similar procedures have been used for other mammalian experiments. The odorant concentration is generally indicated in dilute concentration units parts per million (ppm), parts per billion (ppb), and parts per trillion (ppt) and are usually used with vapor phase concentrations. In previous studies, units based on moles or percent were used and generally refer to concentrations in the liquid phase.

Reported olfactory thresholds

Human

Differences in olfactory sensitivity seem to have a genetic basis in humans as well. The olfactory threshold varies greatly across subjects. Olfactory receptors are determined by a large number of olfactory genes that display a high level of polymorphism and nonfunctional pseudogenes (Cometto-Muniz and Abraham 2008). Because human diseases are the main focus of scientific research, the influence of diseases on olfactory sensitivity in humans has been thoroughly explored in subjects with

obsessive compulsive disorder (Browne *et al.* 2006), Parkinson's disease (Harper *et al.* 2005, Haehner *et al.* 2007, Wu *et al.* 2011), diabetes mellitus and its genetic background (Guthoff *et al.* 2009), dementia and Alzheimer disease (Wysocki *et al.* 1997), schizophrenia (Moberg *et al.* 1999), depression (Ferris *et al.* 2007, Croy *et al.* 2014a), and other various dysfunctions. Human emotions (Larsson *et al.* 2000, Brand and Millot 2001, Pause *et al.* 2001, Havlíček 2008) and personality (Havlíček 2012, Pause 2012) may influence olfactory perception and it has been demonstrated that strong negative emotions can reduce olfactory sensitivity (Croy *et al*. 2014a).

In terms of inter-sex differences studies have indicated that women outperform men in specific olfactory threshold measurements (Brand and Millot 2001, Doty and Cameron 2009). Olfactory sensitivity in women may vary within a few days, differences depending on reproductive state (Lundstrom *et al.* 2006) and during the menstrual cycle (Hummel *et al.* 1991, Doty and Cameron 2009) have been found. A review by Martinec Nováková *et al.* (2014) supported the notion that there is a significant cycle-correlated variation of olfactory sensitivity in women (Hummel *et al.* 1991). Olfactory thresholds differed significantly across the cycle; the lowest thresholds were measured during the ovulatory phase and the highest during the menstrual phase (Navarrete-Palacios *et al.* 2003), in a variety of odorants (social and non-social odors), regardless of their different evolutionary significance (Saxton *et al.* 2008, Martinec Nováková *et al.* 2014). These findings support the claim that changes in olfactory sensitivity are linked to a common effect in odor perception in general (Pause *et al.* 2006, Doty and Cameron 2009). Although sexual orientation might play a role in hypothalamus activation in putative hormones (Savic *et al.* 2001, Berglund *et al.* 2006, Savic and Lindstrom 2008), it can be explained by sexual arousal, an acquired sensitization to a specific compound (Berglund *et al.* 2008). It has also been repeatedly proven that olfactory sensitivity decreases with aging (Ezeh *et al.* 1992, Stevens and Dadarwala 1993, Hummel *et al.* 2007, Guthoff *et al.* 2009). According to numerous studies, the repeated introduction of a target odor (even in a perithreshold concentration) causes a decrease in the olfactory threshold and detection sensitivity (Doty *et al.* 1981, Rabin and Cain 1986, Wysocki and Gilbert 1989, Dalton *et al.* 2002, Mainland *et al.* 2002). The brain synapses strengthen with use (Jancke 2009), and everyday olfactory experiences can improve olfactory performance *via* long-term neuronal plasticity in the olfactory brain regions (Buschhuter *et al.* 2008, Frasnelli *et al.* 2010, Seubert *et al.* 2013). During an investigation in which acetone was used as a target odor, the exposure of experimental subjects to acetone decreased olfactory sensitivity. The ODTs were set at 855 ppm in previously exposed subjects and 41 ppm in non-exposed subjects (Wysocki *et al.* 1997); this was in contrast to increasing sensitivity with experience in investigation cases. This suggests exposure to some substances induces changes in sensitivity, which are specific for this substance (acetone) in particular. The odorant-specific plasticity in the olfactory system is supported by studies that used human steroids as the target odorant. A pronounced decrease in the ODTs of more than four orders of magnitude with repeated exposure was found for the human steroid androstadienone. These experience-dependent changes in threshold were accompanied by a change in perceived odor quality (Lundstrom *et al.* 2003). Androstenone-anosmic subjects can acquire sensitivity to this steroid hormone by repeated exposure, while subjects who are able to detect androstenone can lower their threshold with repeated exposure (Jacob *et al.* 2003, Wang *et al.* 2004).

Amyl acetate was used as a target odor when different methods (general procedure, modified constant stimuli procedure, FC-AML procedure, staircase procedure) for determining the ODT were compared. The average threshold of these methods was about 0.11 ppb (Wise *et al.* 2008). In similar studies, certain ODTs were set as low as 0.29 ppb (acetate esters) (Cometto-Muniz *et al.* 2008), 0.14 ppb (aliphatic aldehydes) (Stevens *et al.* 1988), 2 ppm (hydrogen sulfide) and 1.9 ppm (cis-3-hexen-1-ol) (Jaeger *et al.* 2010), which also contain high concentration results such as 500 000 ppm for carbon dioxide or 175 000 ppm for amyl acetate. Specific ODTs for n-alcohols in humans varied from 2.52 ppb (ethanol) to 0.64 ppb (I-octanol) (Cometto-Muniz and Abraham 2008). A subsequent study on humans set the olfactory sensitivity threshold for different organic substances from 245 ppb (ethyl acetate) to 2.9 ppb (hexyl acetate) (Cometto-Muniz *et al.* 2008). Using 2-ketones as the target odorant, the ODT decreased from 832 ppb (acetone) to 5.5 ppb (nonanone) (Cometto-Muniz and Abraham 2009b). For the use of n-alkyl benzenes as a target odor, the specific detection threshold decreased from 89 ppb (octylbenzene) to 2.5 ppb (butylbenzene) (Cometto-Muniz and Abraham 2009a). A similar research study was conducted with aliphatic aldehydes and

helional as the target odors, and the ODTs decreased from 2.0 ppb (propanal) to the lowest threshold of 0.14 ppb (octanal and helional) (Cometto-Muniz and Abraham 2010). The inter-individual threshold variability ranged between one and two orders of magnitude.

The chemesthesis threshold for pungency occurs in concentrations as low as one and as high as six orders of magnitude above the olfactory threshold (Cometto-Muniz and Cain 1990, Cometto-Muniz and Hernandez 1990, Cometto-Muniz and Cain 1991, 1993, 1994). When the effect of aging on olfactory capabilities was examined, butanol was chosen as the target odor, and the olfactory threshold was set at 60 000/l in elderly subjects and at 2200/l in younger subjects (4 % solution v/v of butanol in DHOH (deionized water) corresponding to 3100 ppm in the air) (Stevens and Dadarwala 1993). Female olfactory sensitivity to various alcohols was evaluated as slightly higher than male olfactory sensitivity (Cometto-Muniz and Abraham 2008). For aldehyde bourgeonal, men were able to detect significantly lower concentrations (13 ppb) than were women (26 ppb) (Olsson and Laska 2010), but according to other odor detectability studies, gender was not a significant factor (Stevens *et al.* 1988). In a number of studies, interindividual variability of about one order of magnitude was found between the most and the least sensitive subjects (Cometto-Muniz *et al.* 2008, Cometto-Muniz and Abraham 2009a,b).

Although setting the olfactory detection threshold in humans seems easier than in other mammalian species, the results of olfactory sensitivity studies differ significantly. Thus, the odor detection threshold is a function of the subject's olfactory sensitivity and the experimental method. Attention must be given to the delivery, control, and reliability of the vapor stimulus in measurements of psychometric functions. When the results with the lowest olfactory threshold set are compared, the lowest detected concentration in aliphatic alcohols and aldehydes. The comparison of individual studies is not conclusive because of the methodological differences in olfactometric and psychophysical techniques.

Although the olfactory thresholds are a function of subject sensitivity and method, only a few studies with directly comparable methods used the same subject and stimulus (Wise *et al.* 2008). The current trend is to present olfactory stimuli in the vapor phase (Cometto-Muniz and Abraham 2008, 2010) instead of the liquid phase as in previous behavioral studies (Stevens and Dadarwala 1993), to obtain the required concentration. The stimulus concentration is most accurate when it is presented in the vapor phase and is calculated from vapor pressures (Cometto-Muniz *et al.* 2003). However, vapor pressure calculated from values taken from the literature may potentially exhibit large differences depending on different literature sources (Stevens and Dadarwala 1993, Cometto-Muniz and Abraham 2010). Therefore, particular computer-controlled vapor delivery devices are currently used to generate and present olfactory stimuli (Cometto-Muniz and Abraham 2008, Cometto-Muniz *et al.* 2008). Gas chromatography quantification of an olfactory stimulus is an indispensable aid today (Cometto-Muniz *et al.* 2008, Cometto-Muniz and Abraham 2009b), but it was not used in earlier studies (Stevens and Dadarwala 1993). The constant stimuli method measures full detection function (Wise *et al.* 2008), while the forced-choice ascending method of limits (Lawless 2010) and the staircase method (Wysocki *et al.* 1997, Linschoten *et al.* 2001, Lotsch *et al.* 2004) provide a reasonable estimate of the average threshold. For individual differences, the constant stimuli method seems to outperform the ascending method (MacMillan 1991) and the staircase method (Linschoten *et al.* 2001, Lotsch *et al.* 2004), which are largely limited (Wise *et al.* 2008).

In the constant stimuli method, the ODT is defined as the halfway point between chance and perfect detection (Cometto-Muniz and Abraham 2008, 2009b), as detectability (detection probability) (Cometto-Muniz and Abraham 2010) or as inverse detectability (Walker *et al.* 2003).

Non-human primates

The sense of smell in primates has been thoroughly examined in comparison to other mammalian species, possibly because primates are closer to humans than any other species. One of the first investigation methods was tested on squirrel monkeys in as early as 1992, and in the following 20 years, various studies focusing on other non-human primate species were conducted (Hudson *et al.* 1992). For olfactory sensitivity, some authors label animals as either "microsmatic" or "macrosmatic"; however, according to some studies (Laska *et al.* 2000b, Smith *et al.* 2004), these terms do not seem to be valid primate descriptors.

An across-species comparison is based on the assumption that New World primates generally are more sensitive than Old World primates. Since the majority of

primate ODT studies were performed in the same laboratory at Linköping University in Sweden, similar olfactometric and psychophysical techniques were used in these studies. The primate subjects were tested using the two-choice instrumental conditioning paradigm (Hubener and Laska 2001, Laska *et al.* 2003). The ODTs were determined by testing the ability to detect a target sample with increasing dilution of an odorant between odorless blank samples. Olfactory stimuli were presented in the gas phase in equimolar concentrations.

One of the first olfactory investigations in pigtailed macaques (*Macaca nemestrina*) determined the specific olfactory threshold for peanut iso-amyl acetate and n-pentanoic acid odors. The animals detected peanut odor in dilutions as low as 1:10 000, and for amyl acetate, the animals detected dilutions from 30 000-fold up to 30 million-fold. The olfactory sensitivity threshold for pentatonic acid ranged between concentrations of 1:30 000 and 1:300 000 (Hubener and Laska 2001).

A study with n-alcohols as target odorants was then carried out in squirrel monkeys (*Saimiri sciureu*) and pigtail macaques (*Macaca nemestrina*). The animals of both species significantly detected concentrations below 1 ppm, and certain individual monkeys even demonstrated thresholds below 10 ppb (Laska and Seibt 2002a). The same methods were used for aliphatic aldehydes (Laska *et al.* 2003), aliphatic esters, and their isomeric forms (Laska and Seibt 2002b). With few exceptions, both species significantly determined concentrations below 1 ppm, and several animals even demonstrated thresholds below 1 ppb (Laska and Seibt 2002b, Laska *et al.* 2003). The detection thresholds for a homologous series of aliphatic esters and isomeric forms were also investigated in spider monkeys. The monkeys significantly detected concentrations below 1 ppm, and in several cases even below 1 ppb (Hernandez Salazar *et al.* 2003). In the case of aliphatic alcohols and aldehydes, the spider monkeys were able to significantly discriminate concentrations below 1 ppm, and certain individual monkeys even demonstrated detection thresholds below 1 ppb (Laska *et al.* 2006b). In accordance with these results, a following comparative study about olfactory detection performance showed a high degree of similarity between the two primate species (squirrel monkeys and pigtail macaques), as well as between these non-human primates and human subjects tested in an earlier study on the same tasks (Laska *et al.* 2005b). Another study that used acyclic monoterpene alcohols and involved squirrel monkeys, spider monkeys (*Ateles geoffroyi*), and pigtail macaques (*Macaca nemestrina*) showed that squirrel monkeys were significantly more sensitive than the other two species; the squirrel monkeys were able to detect this class of odorants at concentrations below 0.1 ppm (Laska *et al.* 2006a). Nonetheless, a particular comparative investigation performed on substances with apparent behavioral relevance (characteristic of putrefaction processes and fecal odor) in spider monkeys, squirrel monkeys, and pigtail macaques did not show any significant differences among these three primate species. All animals significantly discriminated concentrations below 1 ppm, and in several cases, individual animals even demonstrated thresholds below 1 ppt. The detection thresholds for indol in squirrel monkeys and pigtailed macaques and for ethanethiol in spider monkeys represent the lowest values among more than 50 odorants tested to date. These values are in the same order of magnitude as the lowest detection thresholds that have yet to be reported rats and mice (Laska *et al.* 2007a).

As most of these olfactory studies (Hubener and Laska 2001, Laska and Seibt 2002a,b, Laska *et al.* 2003, 2005a, 2006b, 2007a) were conducted in the same laboratory using the same methods and animals, the threshold values are comparable with great reliability. However, there are some methodological difficulties in between-studies comparison. In two of three non-human primate species, only animals of one sex were available for testing, and the number of subjects was small. A similar methodology complication occurs in dogs studies. In contrast to dog and primate studies, the number of subjects in human and rodent studies is high. A food-reward instrumental conditioning paradigm was used in all non-human primate studies, similar to experiments in dogs and rodents (with the exception of Moulton *et al.* 1960, Krestel *et al.* 1984). Differences in methodology within one laboratory can be seen in the number of choices using the instrumental conditioning. In some studies, there was a two-choice paradigm (Laska *et al.* 2003) while in another study the multiple-choice paradigm was used (Laska *et al.* 2007a). To minimize the possibility of adaptation, between-trial intervals were important as well as the descending staircase concentration procedure (increasing dilutions). When some of the odorant classes were not water soluble, other odorless solvents (diethyl phthalate) had to be used (Laska and Seibt 2002b, Laska *et al.* 2003). In

comparison to the number of human ODTs studies, odorants were presented in the liquid phase without direct conduction to the subjects' faces.

These studies demonstrated that spider monkeys, squirrel monkeys, and pigtailed macaques have a well-developed olfactory sensitivity for different classes of odorants, in comparison to another species classified as microsmatic. A similar methodology allows us to collate experimental results between individual species (Table 1). The results show primates are most sensitive to thiols and indols, while pigtailed macaques were the best-scoring species. In contrast, squirrel monkeys and spider monkeys outperformed when aliphatic alcohols and aldehydes were used as the target odorants.

Across-species ODT comparisons seem to support the contention that comparisons of neuroanatomical features or of the number of functional OR genes are only poor predictors of olfactory performance. The ODT studies emphasize an ecological view that tries to correlate chemosensory performance with the behavioral relevance of the subject odorant (Laska *et al*. 2009, 2010).

Dogs

Dogs are capable of detecting and identifying odorant molecules even in minute concentrations (Quignon *et al.* 2005). The sensitivity of canine olfaction is utilized in many areas, such as biological and abiological scent detection (humans, animals, plants, tobacco, accelerants, bank notes, etc.) (Browne *et al.* 2006). The body of papers that focus on the ability of dogs to detect different types of cancers (Welch 1990, Pickel *et al.* 2004, Willis *et al.* 2004, McCulloch *et al.* 2006, 2012, Horvath *et al.* 2008, 2010, 2013, Cornu *et al.* 2011, Sonoda *et al.* 2011, Bomers *et al.* 2012, Ehmann *et al.* 2012, Bijland *et al.* 2013) as well as diabetes (Dehlinger *et al.* 2013), cirrhosis (Bijland *et al.* 2013), and the first signs of an epileptic seizure (Brown and Strong 2001, Strong *et al.* 2002) is growing. The olfaction of dogs used as a diagnostic tool is often as accurate as, or even superior to, standard diagnostic methods. As our environment is becoming more and more polluted, dogs' sense of smell is useful in pollution and contamination detection (Partyka *et al.* 2014), as well as in mold and other microbial growth detection (Kauhanen *et al.* 2002). Despite technical advances, detection dogs are still a very effective and reliable tool in the search for drugs and explosives (Gazit *et al.* 2003, 2005, Gazit and Terkel 2003, Lorenzo *et al.* 2003, Browne *et al.* 2006, Singh 2007, Irrazabal *et al.* 2009, Moore *et al.* 2012).

Dogs' ability to respond to concentrations of odorants, which humans cannot normally detect, has been widely exploited and has led to the belief that the sense of smell in dogs is far superior to that in humans. One would expect that the mechanism and sensitivity of canine olfaction have been thoroughly studied, but that is not the case (Moulton *et al.* 1960). Even the canine's legendary sense of smell or the growing reliance on dogs' sense of smell in relation to threats to life and property has not led to a reliable quantification of canine olfactory sensitivity (Walker *et al.* 2006). Despite significant efforts invested in olfaction principles studies, many unanswered questions regarding olfaction and the use of specially trained dogs remain (Harper *et al.* 2005). Although data derived from laboratory studies might be expected to provide reliable information about olfactory sensitivity, published values show differences that are perhaps among the most extreme reported for any sensory perception (Moulton *et al.* 1960). The main complication in using psychophysical methods lies in the differences in detection performance between individual dogs; these differences seem to be related to behavioral variations (Svartberg and Forkman 2002, Adamkiewicz 2013, Jezierski *et al.* 2014), which we can expect in other species, investigated using psychophysical tests.

A study performed by the Canine Behaviour Centre, Queens University, Belfast, showed that dogs are able to determine the direction of a track with the aid of only five individual tracks (Hepper and Wells 2005). This was the only study to date that has reported differences in olfactory sensitivity between male and female domestic dogs. Male dogs identified the correct direction of a given track more frequently than did female dogs, and younger dogs performed better than older animals (Wells and Hepper 2003). The same research team also confirmed pre- and post-natal learning regarding chemosensory stimuli in puppies (Hepper and Wells 2006). Gender-specific induction of enhanced sensitivity was found in male dogs which generally outperformed female dogs. These findings are contrary to olfactory studies in humans; studies indicate women outperform men with specific odorant substances, such as sex hormones (Brand and Millot 2001, Doty and Cameron 2009). Regardless, no reliable sex differences have been found in dogs (Wells and Hepper 2003) or in humans (Olsson and Laska 2010, Ferdenzi *et al.* 2013).

Table 1. Olfactory detection thresholds for laboratory chemical substances in vapor phase in ppm concentration.

Chemical class	Chemical substance	Human	Pigtail macaque	Spider monkey	Squirrel monkey	Dog	Mouse
Aliphatic alcohols	pentanol	x	0.29	0.0004	0.0004	x	0.00003
	hexanol	x	0.006	0.006	0.006	x	0.0003
	heptanol	x	0.0032	0.0003	0.00031	x	
	octanol	0.00064	0.0048	0.0048	0.048	x	
	propanal	0.002	x	x	x	x	
Aliphatic aldehydes	butanal	x	0.0004	0.039	0.0039	0.00004	
	pentanal	x	0.148	0.00148	0.0148	x	
	heptanal	x	0.0024	0.00235	0.00235	0.00004	
	hexanal	0.00014	0.00052	0.0052	0.052	x	
	ocatanal	0.0014	0.0016	0.00016	0.16	x	
	burgeonal	x	x	x	x	0.000000001	x
Acetate esters	amyl acetate	0.00011	0.14	x	x	0.0000114	
	ethyl acetate	0.245	x	0.036	x	x	0.0000041
	butyl acetate	0.0043	x	0.00006	x	x	
	pentyl acetate	x	x	0.000027	x	x	
	hexyl acetate	0.0029	x	0.00013	x	x	
Carboxylic acids	butanoic acid	x	x	x	x	x	0.000003
	pentanoic acid	x	x	x	x	x	0.000003
Amid acids	panthotenic acid	x	0.0019	x	x	x	x
Nitroalkanes	dimethyl dinitrobut.	x	x	x	x	0.0005	x
Thiols	ethanethiol	x	0.000096	0.00000096		x	x
	butanethiol	x	0.000016	0.00016	0.00016	x	x
	pentanethiol	x	0.00063	0.00063	0.00063	x	x
Thiazolines	trimethylthiazoline	x	x	x		x	40.00
Indols	indole	x	0.00000003	0.0003	0.00000003	x	x
	methyl indole	x	0.000037	0.0000037	0.000012	x	x
Ketones	nonanone	0.0055	x	x	x	x	x
Sulfides	hydrogen sulfide	2.00	x	x	x	x	x
Amino acids	cystein	x	x	0.0013	x	0.0000044	x
	methionine	x	x	0.0011	x	0.000036	x
	proline	x	x	0.002	x	0.023	x
Alkylpyrazines	pyrazine	x	x	27.80	x	0.028	x
	methyl pyrazine	x	x	0.044	x	0.0001	x
	tetramethyl pyr.	x	x	0.00063	x	0.00000092	x
Benzenes	butylbenzene	0.00025	x	x	x	x	x
	octylbenzene	0.00029	x	x	x	x	x
	propylthietane	0.0000000059	x	x	x	x	x
Sulfur-containing volatiles	methylbutyl form.	0.0000000013	x	x	x	x	x
	propylthiethane		x	0.0000074	x	0.00003	x
	butanethiol	0.00000052	x	0.0000026	x	0.00000003	x
	phenylethyl sulfide	0.0000016	x	0.0000012	x	0.00000003	x
	methylbuthyl form.		x	0.0000052	x	0.000003	x
Oxides	carbon dioxide	x	x	x	x	x	700.00

Olfactory sensitivity may also differ between dog breeds. When the additional olfactory receptor gene polymorphism was identified in 20 various breeds, some mutations were found to be breed-specific (Quignon *et al.* 2005, Tacher *et al.* 2005). No study has been published that compared the olfactory thresholds of various dog breeds. A recent study that compared the olfactory performance of Pugs, German Shepherds, and Greyhounds did not determine their ODT either; nevertheless, in an experiment in which the dogs were supposed to alert to various dilutions of the target odor, Pugs significantly outperformed German Shepherds while Greyhounds could not be tested because of a lack of motivation (Hall *et al.* 2015).

The first investigations dealing with canine olfactory sensitivity compared humans and dogs. According to the earliest studies, olfaction sensitivity in dogs is much better than that of humans (Neuhaus 1953, Laska *et al.* 2008a). The next two investigations revealed that the olfaction sensitivity in canines was approximately the same as that in humans (Nicollini 1954, Becker 1962). A later study found that the olfaction sensitivity in dogs was approximately 100 times greater than that in humans (Moulton *et al.* 1960). However, the previously mentioned publications (Neuhaus 1953, Ashton 1957, Moulton *et al.* 1960, Krestel *et al.* 1984) do not provide data that may be relied upon with confidence (Walker *et al.* 2006).

One of the first studies on the olfactory threshold in dogs was conducted by Neuhaus (1953) and compared dogs and humans. The olfactory threshold in dogs for butyric acid and acetic acid was 8 log units below that in humans. Another study, which compared specific olfactory thresholds in dogs and humans, was conducted by Kaise (1969). The olfactory threshold in dogs for clove oil was estimated at approximately 6 log units below that in humans (Laska *et al.* 2008a). The canine ability to detect n-aliphatic acids was investigated by Ashton *et al.* (1957). The results showed individual differences in two dogs. Performance also varied with the target substances depending on the number of carbon atoms in the molecules of both acid groups. The detectable concentrations were approximately 1.54-0.801 log units of molar concentration.

The results of other studies (Nicollini 1954, Becker 1962) performed on dogs differed considerably. Canine and human olfaction sensitivity was compared again, and the results showed that dogs and humans had the same level of olfaction sensitivity. Three years later, Moulton *et al.* (1960) noted canine olfaction sensitivity was 2 log units below that of humans. The study was carried out with only two Labrador hybrids, and a specific olfactory threshold was determined for fatty acids. The results showed significant differences between the two dogs tested but also between the sensitivity of the two fatty acid groups. A later study by Marshall and Moulton (1981) reported similar results. The canine olfaction threshold was found to be 2-4 log units below that of humans. Krestel *et al.* (1984) also conducted a study focused on the comparison of olfaction in dogs and humans, but the results determined a specific threshold for amyl acetate. The dogs were trained to put their heads into a wooden box, into which the odorant was released. The dogs (six Beagles) were motivated and rewarded with water (deprivation by thirst) and punished with an electrical shock. The results presented a specific canine olfactory threshold 2.6 log units lower than that of humans.

About 20 years later, Pickel *et al.* (2004) studied a specific olfactory canine threshold for amyl acetate while dealing with disease diagnostics. He observed surprising values, and the olfactory threshold was set to a concentration of about 1-2 ppt. The next study investigating olfactory sensitivity in dogs was conducted by Walker *et al.* (2006). The target odorant was the same substance that was used by Krestel *et al.* (1984), i.e. amyl acetate. In a relatively small sample of only two dogs (a Schnauzer and a Rottweiler), they found remarkable values (1.9 and 1.14 ppt) that were roughly 30 to 20 000 times lower than the range of thresholds reported in previous studies (Krestel *et al.* 1984). Walker *et al.* (2006) believed their method "find the target", which is based on positive conditioning and includes more natural and non-restrictive conditions outside the laboratory, is the main cause of the difference between their study and studies that use "more conventional methods". These results indicate that canine olfactory sensitivity may be much higher than previously thought (Walker *et al.* 2006).

Dogs that received steroids exhibited a significant elevation in their detection threshold for benzaldehyde and eugenol, and thus it seems that olfactory acuity could also be influenced by hormones (Ezeh *et al.* 1992).

Studies dealing with canine sensitivity in detecting explosive substances are very rarely published. One of the few studies conducted by the Institute for Biological Detection Systems at Auburn University

identified the specific olfactory thresholds for methyl benzoate, cyclohexanone, and nitroglycerin as ranging from ppb to ppt units (Johnston 1999). Laboratory workers from the Bureau of Alcohol, Tobacco and Firearms found that dogs were able to respond to nitromethane diluted in water in concentrations of one to one trillion. However, much lower concentrations were also mentioned in this study (Kury and Strobel 2003). Adequate olfactometry and behavioral control is often lacking in canine olfactory sensitivity studies. However, differences in the design methodologies of canine olfactory sensitivity studies may produce inaccurate comparisons (Johnston 1999).

The results of ODT studies are essentially incomparable. A small number of olfactory sensitivity experiments in dogs were conducted over a long period, and the olfactometric and psychophysical techniques differed substantially. Single experiments focused on different target odorants, and various dog breeds were used as experimental subjects. Unequal behavioral testing was applied, and the preparation of the odorant sample differed across studies, as well as odorant dilution devices. Moreover, the results were often published as a comparison with humans and described only the difference, without a specific concentration. In general, ODTs in dogs were distinctly the lowest when amyl acetate was used as a target odorant (Walker *et al.* 2006) although the author himself admits the possibility that it is caused by their new methodology.

Similar to other ODT psychophysical experiments, most substantial between-studies differences are found in olfactometer design and test procedure. Descending concentration testing can enhance the absorption effect and provoke olfactory adaptation, so ascending concentration testing is usually preferred (Gostelow *et al.* 2001). As in non-human primate psychophysical experiments, dog experiments are based on operation conditioning; however, in contrast with olfactory studies in primates, the odorant dilution devices differ (Shepherd 2004, Craven *et al.* 2010). A substantial difference in methodologies can be found even between experimental designs of canine studies and huge differences in results in ODT concentrations spring there. According to the latest experimental approaches, the absence of any deprivation during training (physical pain, lack of water or food), as well as the method of target odorant detection (stationary odorant chambers or active finding of the target), causes differences in orders of units (Walker *et al.* 2006, Craven *et al.* 2009). Ascending staircase (decreasing dilution) of odorant concentration is always used in canine experiments, as well as in primates, but the emphasis is placed on the piecemeal descending staircase (increasing dilution) of the concentration to avoid olfactory adaptation by the subjects (Walker *et al.* 2006).

Rodents

Rats (*Rattus rattus*) have a highly developed ability to detect and identify odorants in minimal concentrations (Quignon *et al.* 2005). Although, to date, sniffer dogs remain a still indispensable and very effective means of explosive detection (Moore *et al.* 2012), African giant pouched rats (*Cricetomys gambianus*) have been trained to detect buried landmines (Corcelli *et al.* 2010, Poling *et al.* 2011) and are able to detect tuberculosis (Mahoney *et al.* 2012, Mgode *et al.* 2012). One of the basic factors influencing olfactory acuity is the animal's feeding state. According to a study by Aime *et al.* (2007), food-deprived rats exhibited increased detection at low concentrations, which led to the conclusion that olfactory sensitivity increases in food-deprived animals (Aime *et al.* 2007). Olfactory performance improves with repeated exposure to a particular substance in other mammalian species as well as in rats (Doty and Ferguson-Segall 1989, Wilson 2000, Wilson and Stevenson 2003) and mice (Wang *et al.* 1993, Yee and Wysocki 2001). One of the first olfactory sensitivity studies performed in mice (*Mus musculus*) focused on the absolute detection threshold for ethyl acetate, which was set below 0.41 ppt. When the same methods are used, this value is similar to that obtained in rats (*Rattus rattus*) (Dalton *et al.* 2002). Laska *et al.* (2007b) investigated the ability of discrimination between odorant pairs, first with homologous series of aliphatic aldehydes. The animals were able to discriminate between two odorant pairs when the stimuli were presented at concentrations of 1.00, 0.01, and 0.001 ppm, and mice also have an excellent ability to discriminate between structurally related aliphatic odorants. The mice were also able to distinguish between 50 stimuli that were presented at a gas phase concentration of 1 ppm. The same laboratory later examined the ODTs, and aromatic aldehydes were used as the first target odorants. When all seven stimuli were considered, the mice detected concentrations as low as 0.01 ppm from the solvent, and with bourgeonal, the animals detected concentrations as low as 0.1 parts per quadrillion, which constitutes the lowest olfactory detection threshold value reported in this

species to date (Larsson and Laska 2011).

In a subsequent study, eight structurally related aliphatic C-6 alcohols and aldehydes were used as the target odorant, and all mice detected concentrations below 0.03 ppm. With three of the substances, the best-scoring animals were even able to detect concentrations below 0.03 ppb (Laska *et al.* 2008a). Further comparisons suggest that odor structure-activity relationships are substance class-specific and species-specific (Can Guven and Laska 2012).

ODT studies in rats have also presented results as volume percentages, which make it difficult to compare these studies with previous studies. The detection threshold for CO_2 was estimated at about 700 ppm (Ferris *et al.* 2007).

When microsmatic and macrosmatic mammalian species were compared, mice or rats were used as the subject organism several times in the psychophysical laboratory of Linköping University in Sweden, which make the results at least partially comparable (Table 1). The same methodological principles were a significant advantage in rodent experiments (almost exclusively in mice), similar methodologies found in non-human primates, but lacking in other mammalian ODT studies. The same methodological rules were followed by using automated liquid-dilution olfactometer, near-odorless diethyl phthalate as a solvent, the instrumental conditioning procedure, and the increasing dilution of the target odorant. An important point is the choice of experimental subjects: an outbred strain of mice was used for the experiments as the mice's genetic background is more similar to wild-type mice than that of inbred strains (Laska *et al.* 2007b, Laska *et al.* 2008a, Larsson and Laska 2011, Can Guven and Laska 2012). In rats, target odorants were chosen to investigate the behavioral context, and the results suggested the behavioral relevance of an odorant plays an important role as a determinant of a species' olfactory sensitivity. The across-species experiments in mice allow us to compare the ODT concentrations with some other mammalian species, primarily non-human primates. In general, mice are more sensitive to alkyl pyrazines, amino acids, and aliphatic esters and to aliphatic aldehydes, where the lowest ODT values were reported in this species thus far. Mice were able to detect smaller concentrations than non-human primates when six sulfur-containing volatiles known as components of the odors of natural predators of the mouse were used. When aliphatic alcohols are used, the ODTs in mice are equal to ODTs in humans and non-human primates.

Other mammalian species

In other mammalian species, olfactory sensitivity research is lacking substantially and is mostly confined to studies focused on a number of olfactory cues the subject can easily distinguish. Studies have investigated the South African fur seal (*Arctocephalus pusillus*) (Laska *et al.* 2008b, Laska *et al.* 2010), the Asian elephant (*Elephas maximus*) (Arvidsson *et al.* 2012), and the short-nosed fruit bat (*Cynopterus sphinx*) (Ganesh *et al.* 2010, Zhang *et al.* 2013). Studies dealing with olfactory detection thresholds in other mammalian species are very rare. The only study of greater significance was carried out using Göttingen minipigs (*Sus scrofa domestica*). The ODTs for ethyl acetate and ethanol were determined as a concentration as low as 5 ppm (Sondergaard *et al.* 2010), which is far from the lowest ODT reported in other mammalian species, but it is important to point out the inconsistencies in methodology. As experiments in these species are still in their infancy, they are focused on the ability of determination, in contrast with olfactory threshold experiments in primates, dogs, or rodents. Therefore, a between-species olfactory sensitivity comparison based on these studies is not possible.

Between species comparison

The quantitative structure-activity relationship (QSAR) is clearly described by Cometto-Muniz and Abraham (2008, 2009a,b, 2010) and Cometto-Muniz *et al.* (2008) and a significant positive correlation between ODTs and carbon chain length was found in other mammalian species (Laska and Teubner 1998, Laska *et al.* 2000a, 2008a, Laska and Hubener 2001, Laska 2005, Arvidsson *et al.* 2012, Can Guven and Laska 2012). In an inter-species comparison study that used six sulfur-containing components of odors of natural mice predators, 12 subjects were able to detect concentrations below 0.01 ppm; when four of these odorants were used, the best-scoring subjects were able to detect even concentrations below 10 ppt. In this study, the mice were more sensitive to the tested odorants, and olfactory sensitivity did not differ substantially among the human subjects.

The evidence of a low specific olfactory threshold in squirrel monkeys and humans for carboxylic acids was provided and supports the assumption that human and non-human primates may share common

principles of odor quality perception (Laska and Teubner 1998). Another investigation that compared non-human primates and rodents was performed with substances with apparent behavioral relevance (characteristic of putrefaction processes and fecal odor) in spider monkeys, squirrel monkeys, and pigtail macaques. No significant differences between these three primate species were found. All animals significantly discriminated concentrations below 1 ppm, and in several cases, individual animals even demonstrated thresholds below 1 ppt. The ODTs for indol in squirrel monkeys and pigtailed macaques and for ethanethiol in spider monkeys represent the lowest values among more than 50 odorants tested to date. These values are in the same order of magnitude as the lowest detection thresholds that have yet to be reported in rats and mice (Laska *et al.* 2007a). Next, a study testing primates and mice was conducted with three female spider monkeys. They were able to detect aliphatic alcohols and aldehydes at concentrations below 1 ppm, and six of the eight stimuli were detected at concentrations below 0.1 ppm by the animals with the highest olfactory sensitivity. Mice even outperformed non-human primates with ODTs for aliphatic alcohols below 0.01 ppm (Lotvedt *et al.* 2012).

The behavioral relevance of trimethylthiazoline (a volatile component of the anal gland secretion of the red fox) was the main issue of between-species comparison between rats and three primate species. The three primate species, which are all non-prey species of the red fox, were able to detect concentrations in ppb units, which do not rank among the lowest olfactory thresholds reported for these species. Rats, a natural prey species of the red fox, were able to discriminate concentrations between 0.04 and 0.10 ppt, which is by far the lowest olfactory detection threshold for an odorant reported in rats to date (Laska *et al.* 2005a).

Olfactory sensitivity for alkyl pyrazines in mice and spider monkeys was tested in a comparative study (Laska *et al.* 2009). The spider monkeys were able to detect five stimuli at concentrations below 1 ppm, and with one stimulus, they were able to identify concentrations even below 1 ppb. With all six alkyl pyrazine stimuli, mice were able to detect concentrations below or equal to 0.1 ppm, with the best-scoring individuals detecting concentrations below or equal to 0.1 ppb; these results indicate that mice may be more sensitive than spider monkeys. Another comparison of the detection thresholds between mice and spider monkeys was performed for three amino acids. The best-performing spider monkeys detected concentrations below 1 ppb. All the mice detected concentrations equal to or below 0.1 ppm, and the best-scoring animals were able to detect concentrations even below 0.1 ppb (Wallen *et al.* 2012). The results of these two studies indicated that mice were more sensitive than spider monkeys. In an additional comparison study that included humans, spider monkeys, and mice, six sulfur-containing components of the odors of natural predators of mice were used as target odors. The spider monkeys were able to detect concentrations below 0.01 ppm, and four of these odorants were detected at concentrations below 10 ppt by the animals with the highest olfactory sensitivity. In this study, the mice proved to be more sensitive to the experimental odorants; however, the human subjects did not differ significantly.

When olfactory detection thresholds for seven aromatic aldehydes were determined, no general differences between olfactory sensitivity in humans and that of spider monkeys were observed (Kjeldmand *et al.* 2011). Both species detected concentrations lower than 1 ppm for all odorants, and certain individuals even distinguished concentrations lower than 1 ppb for several odorants.

These results support the assumption that the behavioral relevance of an odorant may be an important determinant of a particular species' olfactory sensitivity. In the future, it might be useful to select target substances used in ODT comparisons by their behavioral relevance to each of the investigated species.

Conclusions

As a result of intensive research activities in physiology, genetics, anatomy, and behavior, knowledge surrounding the mechanisms underlying olfactory perception has increased significantly within the last two decades. Nevertheless, many questions remain open despite the immense progress made. Among these questions are those that deal with olfactory thresholds and olfactory system sensitivity. Physiological principles that determine a specific olfactory sensitivity are still unclear, and after several papers that deal with the behavioral testing of various mammalian species were reviewed, it is still not possible to conclude which anatomical or physiological characteristics are responsible for higher or lower thresholds to specific substances.

An overview of olfactory sensitivity in most studied mammalian species is presented here, together

with basics of olfactory perception and olfactory sensitivity factors. The results of the more than 40 studies presented provide further evidence of low specific olfactory thresholds in mammalian species. These research findings lend further support to the suggestion that genetic or neuroanatomical between-species comparison cannot be taken as a reliable predictor of olfactory performance.

According to the current research developments, scientific attention is increasingly focused on how olfactory sensitivity changes are associated with diagnosis of human diseases (Wu *et al.* 2011, Guthoff *et al.* 2009, Moberg *et al.* 1999, Croy *et al.* 2014b). The rise of this field of study is closely related to the development of high-resolution magnetic resonance (Welge-Lussen *et al.* 2009, Toledano *et al.* 2012, Croy *et al.* 2014c) and event-related potentials recording (Kayser *et al.* 2011). Another rapidly developing research area is closely linked to the between-species comparisons described in this review, and investigations focused on olfactory gene expression (Quignon *et al.* 2005, Tacher *et al.* 2005) not only in mammals (Laberge and Hara 2004).

As is made clear in this article, no studies have demonstrated a direct connection between olfactory sensitivity and an absolute number of specific olfactory receptors, the density of ORs in the olfactory epithelium, or the size and quality of the olfactory structures in the brain. An ecological view of olfactory sensitivity correlated with the behavioral relevance of odor stimuli offers a future approach in the significance of olfaction in mammalian species. The detectability of odorants may also be affected by their behavioral relevance and frequency of occurrence in the environment of the receiving subject. Future behavioral research in the field of specific olfactory sensitivity should focus on differences associated with species, breeds, sex, previous exposure, and behavioral relevance. A uniform comparable methodology of etho-physiological experiments has not been introduced. In the future, more integration of component studies should be followed, leading to a uniform methodological approach.

Conflict of Interest

There is no conflict of interest.

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