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Research report

Peripheral adaptive filtering in human olfaction? Three studies on prevalence and effects of olfactory training in specific anosmia in more than 1600 participants

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ABSTRACT

Selective processing of environmental stimuli improves processing capacity and allows adaptive modulation of behavior. The thalamus provides an effective filter of central sensory information processing. As olfactory projections, however, largely bypass the thalamus, other filter mechanisms must consequently have evolved for the sense of smell. We investigated whether specific anosmia – the inability to perceive a specific odor whereas detection of other substances is unaffected – represents an effective peripheral filter of olfactory information processing.

In contrast to previous studies, we showed in a sample of 1600 normosmic subjects, that specific anosmia is by no means a rare phenomenon. Instead, while the affected odor is highly individual, the general probability of occurrence of specific anosmia is close to 1. In addition, 25 subjects performed daily olfactory training sessions with enhanced exposure to their particular "missing" smells for the duration of three months. This resulted in a significant improvement of sensitivity towards the respective specific odors.

We propose specific anosmia to occur as a rule, rather than an exception, in the sense of smell. The lack of perception of certain odors may constitute a flexible peripheral filter mechanism, which can be altered by exposure.

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1. Introduction

Selective processing of environmental stimuli facilitates adaptive modulation of behavior and improves processing capacities by focusing on relevant information. Filtering mechanisms can be divided into peripheral and central ones. Peripheral filters depend on the receptive properties of sensory cells. Human auditory hair cells, for instance, do not respond to ultrasound very well, shielding our ears from such acoustic input. Another example is the variation of receptor density of tactile nerves in different parts of the body, which, for example, provides very high discrimination ability in the fingertips. Such peripheral filters work similarly but also rather uniformly within a given species. Central filter mechanisms, on the other hand, are much more flexible. They are based upon complex top–down interactions, allowing precise attenuation of selective attention in accordance with the needs of the body. The thalamus is commonly regarded as the bottleneck of central sensory information processing, representing a relay that gates sensory information to the cerebral cortex in wakefulness while suppressing this flow of information during sleep for instance. Thalamic gating and thalamic-cortical loops focus attention. Furthermore, thalamo-cortical pathways are involved in sleep-to-wake transitions if significant environmental stimuli occur (McCormick & Bal, 1994). In olfaction, however, which evolutionarily preceded thalamic evolvement, the thalamus is largely bypassed and cannot operate as a gating agent. Some other phylogenetically ancient filter mechanisms should consequently be available for the sense of smell and might still be conserved in humans. Some of the gating functions otherwise performed by the thalamus are executed by the olfactory bulb (Kay & Sherman, 2007).

We investigated whether specific anosmia, the puzzling condition of being unable to perceive a specific odor in otherwise normal olfactory function, represents an effective peripheral filter of olfactory information processing.

Some of the first systematic descriptions of specific anosmia, also known as partial anosmia or odor blindness, extend back to 1893, where individuals were described who were able to smell all odors except vanilla [(Reuter, 1893) cited by (von Skramlik, 1926)]. Since that time it has been considered a rather rare phenomenon with a prevalence of as little as .1% for skunk smell (butyl mercaptan), for instance (Patterson & Lauder, 1948). In numerous studies, the rate of specific anosmia depended on the odor investigated: Specific anosmia to isovaleric acid, with a low molecular weight, varies between 2 and 3% (Whissel-Buechy & Amoore, 1973) (Amoore, 1977), whereas the prevalence of specific anosmia towards the larger molecules of pentadecalactone varies between 7 and 12% (Amoore, 1977; Whissel-Buechy & Amoore, 1973).

Research on specific anosmia was very active until the late 1970s. However, after the exciting first findings, results became more predictable: For nearly all tested odors, some specific anosmics could be identified. Thus, each odor needed to be tested in numerous subjects in order to capture the relatively small prevalence rate – apparently, as long as enough subjects were tested, there would be always some specific anosmia to any odor. Up to now, specific anosmias have been reported for about 60 odorants [for example see (Amoore, 1967; Hirth, Abadanian, & Goedde, 1986; Kirk & Stenhouse, 1953; Patterson & Lauder, 1948; von Skramlik, 1926; Triller et al., 2008; Whissel-Buechy & Amoore, 1973)], and presumably many more would emerge if that line of research were more active. At least 2467 active chemicals with an odor have been described (Arctander, 1969). If indeed almost all smells are possible targets of specific anosmias, and if the overlap of specific anosmia is rather low, it seems plausible that everybody should have a specific anosmia to some odor. As a consequence, while the frequency of anosmia to any single odor is rather small, the general phenomenon of specific anosmias seems quite normal: Specific anosmia might be considered to be the rule, rather than the exception of olfactory processing. There are some publications supporting this view: The prevalence of specific anosmia to at least one out of six odors was reported to be as high as 45% (Hirth et al., 1986), and the prevalence of specific anosmia to at least one out of 10 odors as high as 60% (Triller et al., 2008). A rather liberal definition of non-perception in those studies may have led to an overestimation of prevalences, but the basic notion remains to be taken seriously: the likelihood of being anosmic to any odor out of a large number is much higher than the probability to suffer from specific anosmia to one particular odor.

Among other factors, specific anosmia may be due to a change in secretion and composition of the mucus on the olfactory epithelium and expression of olfactory receptors. A mucus-related change in perception of odors may affect certain groups of molecules more than others, e.g., in relation to lipophilicity. The lack of certain receptors on the other hand results in specific anosmia for any odor that is mainly coded by the respective receptors. In theory, humans may be able to differentiate between as many as one trillion smells (Bushdid, Magnasco, Vosshall, & Keller, 2014), which are encoded from a relatively small number of different olfactory receptors, coded by about 400 functional olfactory receptor genes (Glusman, Yanai, Rubin, & Lancet, 2001). However, only some of the olfactory receptor genes are expressed. Examination of anatomical sections from 26 donators recently showed that humans on average express only about 26% of the olfactory receptor genes (range 18–51%), and so far the underlying selection process – that is, which olfactory receptors are expressed and which are not – is unknown (Verbeurgt et al., 2014). This apparently normal lack of olfactory receptors makes specific anosmia to some odors in any person likely. In addition, animal studies have revealed that receptors of the mouse nasal mucosa undergo regeneration approximately every 1–4 months (Graziadei & Monti-Graziadei, 1978). This could engender slow adaptation to the olfactory environment by adjusting olfactory receptor gene expression to the requirements of the individual. Such changes could, for instance, be triggered by learning or by hormonal changes (Chopra, Baur, & Hummel, 2008).

A methodological issue in specific anosmia research concerns the cutoff criterion. Odors typically bind to more than one receptor: olfaction is accordingly based on pattern recognition. As a consequence, non-expression of specific receptors will not lead to total non-perception of an odorous molecule as long as bindings to other receptors are preserved.

Furthermore, high concentrations of most odorous molecules co-activate the trigeminal system (Croy et al., 2014). Therefore, in a person with specific anosmia to a given odor, a pronouncedly higher detection threshold for this smell, as compared to other odors, should be expected, rather than no response at all. Thus, the definition of a critical threshold is essential to define when perception of a specific odor is impaired.

Depending on the conservativeness of such a cutoff criterion, specific anosmia will be found more or less frequently. As an example, for androstenone, reported frequencies of anosmia range from 1.8% to 75% (Triller et al., 2008). In order to solve this problem, two standard deviations from the concentration perceived in the population has been suggested as cutoff (Amoore, 1967). However, this implies a global prevalence of specific anosmia of 2.5% for any odor that has a normal distribution of olfactory thresholds. In a better approach could define specific anosmia in terms of a constant multiple of the concentration corresponding to normal olfactory function (Herberhold, 1975). For the present studies, we set the cutoff criterion for specific anosmia to one hundred times the mean odor concentration for those who can detect the odor. Notably, this criterion is more conservative than the previously cited one (Amoore, 1967), which defined anosmic perception thresholds as ten times more concentrated than the mean for those who can detect the odor.

Our aim was to investigate peripheral filtering of olfactory information. We therefore compared the rate of specific anosmia of 20 odors differing in molecular structure and size as well as in percept in three consecutive studies: The first study, with 1600 participants, allowed an estimation of the general prevalence of specific anosmia. The rates of specific anosmia per odor as well as the basic assumptions for estimating these rates were evaluated in the second study. The third study explored whether specific anosmia may be addressed by systematically repeated exposure to the respective odors, in order to elucidate the role of specific anosmia as a potentially adaptive filter of olfactory information processing.

2. Study I

2.1. Material and methods

All studies followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and were approved by the Ethics Committee of the Medical Faculty of the "Technische Universität Dresden" (application number EK40022009). All participants provided written informed consent.

2.1.1. Participants

Twenty odors were tested with 200 participants for each odor. In total, 1600 volunteers were examined and each subject was tested for specific anosmia to two or three odors. Thus, participants were divided into 8 groups (a through h) who were presented with identical odor samples each. 188 out of the entire sample of 1600 volunteers were retrospectively excluded from further evaluation due to reduced general olfactory performance, as assessed by the "Sniffin Sticks" 16-item identification test (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). Final analyses included data of the remaining 1412 participants (869 females, 543 males, age range 18–72 years; mean 26.4, ±6.4 years SD). Volunteers received confectionary as a recompense for participation.

2.1.2. Material

Each odor was presented in 7 dilution steps, starting with a concentration of $1{:}10^{7}$, with consecutive dilutions containing ten times the amount of odorant than the preceding one. The highest concentration was accordingly 1:10 for each odor. All odors were diluted in 1,2-propanediol [CAS Registry Number, 57-55-6]. Approximately 4 ml of each dilution was presented in a 50 ml glass bottle with a diameter of 6 cm. Brown glass was used in order to prevent visual distraction. Among the 20 different odors, seven were associated with food, three with flowers, four were musky odors, two reminiscent of sandalwood and four represented other types of smells. Names and characteristics of the odors are displayed in Table 1. Seven bottles contained dilution only.

2.1.3. Procedure

After having been informed about the study and provided written consent, participants underwent olfactory testing with the Sniffin Sticks 16-item odor Identification test. Normosmic function was assumed if participants correctly identified at least 12 out of 16 odors (Hummel et al., 2007). Afterwards testing for specific anosmia took place.

The procedure always started with the lowest concentration of an odor, and continued with stepwise increasing concentrations. In each step, participants were presented with two bottles in a random sequence, one containing odorant, and the other one dilution only. In a forced choice paradigm, subjects were required to decide which bottle contained the odor. This test was repeated twice, or, on demand, three times at the most. If one of the answers was incorrect, testing continued with the next higher concentration. The procedure was repeated until correct discrimination between odor and dilution in all presentations of one concentration; this was established as the individual threshold. This fast approach has the advantage of high sensitivity, however specificity is low. In case of two repetitions per odor concentration, the statistical chance of normosmia for the highest dilution level is 25%, and the chance of anosmia in the lowest concentration is 3%. As a consequence, the rate of specific anosmia is likely to be under- rather than overestimated.

Each participant was tested with two or three odors (Table 1). For 11 of the odors, participants were additionally asked to rate their individual perceptions of the highest odor concentration with respect to intensity and pleasantness, using a scale from 0 through 10 (intensity: 0 = not perceived, 10 = extremely intense; pleasantness: 0 = extremely unpleasant, 10 = extremely pleasant).

2.1.4. Statistical methods

SPSS 20 (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis. For each odor, the concentration of normal perception (CNP) was determined as the dilution level at which at least half of the subjects were able to perceive. The

Table 1 – Odors tested for specific anosmia and rate of specific anosmia per odor.* additional intensity and pleasantness ratings in the highest concentration. Letters in superscript indicate subsamples of subjects odors were presented to.

Odor	Category	Description	Molecular weight in Dalton	Number	Percentage
Trans-2-nonenal*[a]	Food	Cucumber like	85.17	2	1.20
3-Hydroxy-2-methyl-4-pyrone*[b]		Sweet, malty	126.11	21	12.10
2,3-Butanedione*[c]		Buttery, fatty	86.10	0	.00
I-carvone[f]		Minty	150.22	11	6.20
Isoamylacetat[f]		Sweet, fruity	130.18	0	.00
Citralva[g]		Citrus	149.23	10	5.70
1-Octen-3-one*[h]		Metallic, mushroom	126.20	9	5.20
Isobutyraldehyde[h]		Honey	72.11	2	1.10
Mean rate of anosmia to food odors					3.94
Lyral*[d]	Flower	Flowery	210.32	21	11.20
Phenyl ethyl alcohol[e]		Flowery	122.17	0	.00
Geraniol[e]		Flowery	154.25	1	.50
Mean rate of anosmia to flower odors					3.9
Pentadecanolide*[b]	Musk	Musky	240.38	10	5.70
Muscone*[d]		Musky	238.41	27	14.40
Galaxolide[g]		Musky	258.40	10	5.70
Mean rate of anosmia to musk odors					8.6
Sandranol*[c]	Sandalwood	Sandalwood	208.34	5	3.10
Bacdanol*[c]		Sandalwood	216.41	33	20.40
Mean rate of anosmia to sandal wood odors					11.75
Isovaleric acid *[a]	Other	Sweet unpleasant	102.13	5	2.90
Cedrylmethylether*[b]		Wood	236.39	4	2.30
1,8-Cineol[e]		Etheric, medical	154.25	0	.00
Salicylic ester[f]		Pleasant	228.24	17	9.60
Mean rate of anosmia to other odors					3.7

concentration of specific anosmia (CSA) was established as CNP/10^2. In other words: Specific anosmia was established as the inability to perceive an odor at a concentration 100 times stronger than the concentration that half of the subjects perceived. The rate of specific anosmia was determined for both single odors and odor categories. The impact of sex on specific anosmia was tested with a Chi-Square test, the impact of age with a t-test.

Whether specific anosmia leads to a different perception of odors at the highest concentrations was tested with a linear mixed model approach, where individual repetitions of odors were taken into account. The effect of specific anosmia (with three values: specific anosmia [concentration $\leq$ CSA], hyposmia [CSA < concentration < CNP], normosmia [concentration $\geq$ CNP]) on intensity and pleasantness was calculated, odor quality served as covariate. Fixed main and interaction effects were calculated. The threshold for post hoc testing was set to 90% confidence interval, in order to capture effects in the low sample size of subjects with specific anosmia per odor.

In order to assess the relationship between specific anosmia and molecular size, the rate of specific anosmia per odor was correlated with molecular size of the odorant, using a parametric Pearson correlation.

The probability for exhibiting two or more specific anosmias was calculated for odors tested in one subject group. From this, the mean probability of overlap was estimated. These data were used to estimate the likelihood that a person would exhibit specific anosmia to any of a certain number of odors. Probability of being anosmic to at least one out of n odors was calculated by use of binominal function, adjusted for the mean overlap.

2.2. *Results*

2.2.1. *Rate of specific anosmia per odor*

For all except four odors, there was at least one person who fulfilled the criteria for specific anosmia (see Fig. S1). Rate of specific anosmia varied from .5% to 20.4% and was significantly related to molecular weight of the odorants (r = .50, p = .023). Heavier substances had a higher likelihood for anosmia than lighter ones (see Fig. 1 and Table 1). Comparison

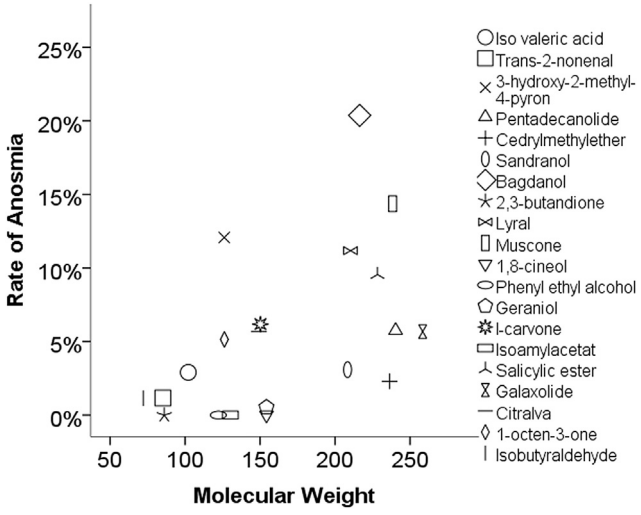

Fig. 1 – Coherence between rate of specific anosmia and molecular size of the 20 odors. Odors with higher molecular size had a significantly higher rate of specific anosmia.

of categories indicated that food and flower odors had a lower rate of specific anosmia compared to sandalwood and musk odors. However, the limited number of odors per category does not allow statistical inference.

2.2.2. *Prevalence of specific anosmia*

The overlap of anosmia varied depending on the odor (Fig. S2); 74% of the participants with specific anosmia were anosmic to only one of the tested substances. Mean probability of exhibiting specific anosmia to any of the 20 odors was 5.4%, and 4.0% when corrected for the overlap. From the corrected frequency of anosmia, the probability of specific anosmia to odors within a larger range of smells can be estimated by use of the binominal formula. This procedure yielded a prevalence value of specific anosmia to at least one of the 20 odors of 51.9%.

Based on the same presumptions, the prevalence for specific anosmia to at least one out of 50 odors amounts to 86.9% and 98.3% if 100 odors are taken into account (see Fig. 2). However, these numbers only give a preliminary impression as odors were tested in series, and the overlap of specific anosmia between odors was very roughly estimated. There was a certain chance of false negative answers (25% for the lowest dilution step to 4.4% for the highest dilution step) and the mean error rate was calculated to 5.9% (=error rate per odor specific cutoff × prevalence of anosmia per odor). However, even when this error was taken into account, results remained substantially the same (see Fig. 2).

2.2.3. *Effect of age and sex*

Both variables explained only a small portion of variance of specific anosmia. There was a significant, yet small, effect of sex, with women showing a slightly reduced rate of anosmia compared to men (women 4.6% *vs.* men 6.5%; $p = .017$, Chi-Square = 5.8; phi = .041). Furthermore, participants with specific anosmia were slightly older compared to participants with unimpaired olfaction for the odors tested (27.6 ± 6.4 years SD *vs.* 26.2 ± 6.6 years SD; $t = 2.5$, df = 1411, $p = .013$).

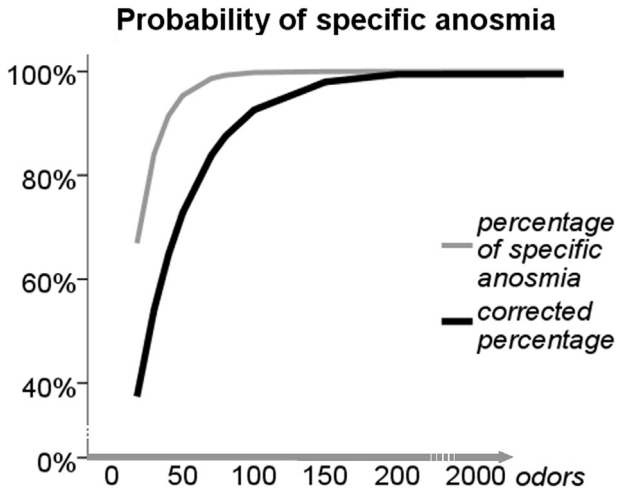

Fig. 2 – Probability of specific anosmia in relation to the number of odors. For a higher population of odors (x-axis), the probability for specific anosmia towards at least one of the odors approaches 100%. The gray line shows the estimation based on the calculation of the mean and overlap of specific anosmia in 1412 people from study I. The black line shows the corrected percentage based on study II (N = 99). The dashed lines represent the false negative error rates for both estimations.

2.2.4. *Perception of intensity and pleasantness*

The highest concentration of eleven out of the 20 odors was evaluated by all participants with respect to intensity and pleasantness. Participants with specific anosmia had significantly different percepts of the respective odors at suprathreshold concentrations. For intensity, a significant main effect of specific anosmia was established [$F(2,1059.6) = 4.0$, $p = .018$]. Post hoc tests revealed that subjects with specific anosmia rated the odors as less intense than did normosmic participants ($p = .001$) and compared to subjects in the intermediate group ($p = .001$). There was no significant difference between normosmic participants and those in the intermediate group ($p = .067$). No significant main effect of specific anosmia [$F(2,1098.4) = 1.9$, $p = .15$] was found for pleasantness, but a significant interaction between specific anosmia and odor was observed [$F(2, 608.3) = 3.9$, $p = .022$]. Specific anosmia was not associated with overall enhanced or reduced pleasantness of odors, but it affected the hedonic qualities of odors differentially. In contrast to individuals who can smell those particular odors, pleasantness scores of subjects with specific anosmia were significantly higher ($p < .1$) for bacdanol and lyral, and significantly lower for 3-hydroxy-2-methyl-4-pyron.

2.2.5. *Conclusion*

The likelihood of specific anosmia towards one out of 100 odors was estimated to be 98.3%. However, as overlap of specific anosmias to various odors was not taken into account and thus, this finding may be overrating the occurrence of specific anosmia, study 2 was carried out.

3. Study II

3.1. *Material and methods*

In order to get a better overview about the overlap between specific anosmias towards different odors, 99 normosmic subjects (68 females, 31 males; age range 18–33 years, mean 24.2, SD 3.4 years) were tested. None of the participants were enrolled in study 1. Volunteers received a moderate amount of money for participation.

Assessment of normosmia, the battery of 20 odors and their concentrations, odor specific cutoff thresholds, as well as procedures were the same as in study one.

The investigation protocol was divided into two sessions. In each session, participants were tested for specific anosmia to 10 out of the 20 odors. Order of odor presentation was randomized across participants and sessions. Thus, as opposed to study one, every subject was presented with all 20 odors.

The odor specific cutoff thresholds for specific anosmia were taken from study one. The reliability of values for specific anosmia was computed by parametric odorwise

correlation of the rate of specific anosmia obtained from studies one and two. The mean overlap of specific anosmia was calculated. This data was used for a new estimation of the rate of anosmia to a varying number of odors, as described in study one.

3.2. Results

3.2.1. Reliability of specific anosmia

Comparison of the odorwise rate of specific anosmia between studies I and II revealed good coherence ($r = .65$, $p = .002$).

In addition to specific anosmias established in study one, there was one participant in study II with specific anosmia to 2,3-butanedione, and one to iso-amylacetate. Taken both studies together, for each of the 18 out of 20 odors tested there was at least one person with specific anosmia.

3.2.2. Prevalence of specific anosmia

In 66% of the 99 participants, no specific anosmia to any of the 20 odors was found; 26% exhibited specific anosmia to one of the odors, 5% to two and 3% to three or four odors. No subject was specifically anosmic to more than four odors. Mean probability of specific anosmia, corrected for the overlap, was 2.3% per odor. The prevalence for specific anosmia derived from this result was a little below that in study I (Fig. 2). However, extension of the range of odors to 200 yields the prevalence for specific anosmia of 99.0%, implying that the probability of specific anosmia to at least one out of 200 odors approaches 1.

Similar to study 1, the error of false negative results did not impact the results substantially. However, the within-odor dependencies were not taken into account. It is thus possible that specific anosmia to one odor increases the probability of specific anosmia to a similar substance (Amoore, 1967). Although this dependency is not easy to predict, molecular structure may well determine the presence of specific co-anosmia (Triller et al., 2008).

Based upon the conservative assumption that we overestimated the overlap-corrected mean rate of specific anosmia by 100%, data was recalculated and yielded the corrected number of 350 instead of 200 odors to be required for the 99.5% probability of specific anosmia to at least one of the substances.

3.2.3. Conclusion

The computed likelihood of specific anosmia was smaller than in the previous study, but still approached 1, when based upon a large number of odors.

4. Study III

4.1. Material and methods

In 25 normosmic participants (10 men, 15 women, age range 20–40 years, mean age 24.9 ± 4.3 years SD) with specific anosmia, the effect of olfactory training was tested. Participants were recruited from study I and were remunerated for participation. Most of the participants ($N = 15$) were anosmic to musk odor, five to lyral, two to cedrylmethylether or pentadecanolide, respectively, and one person exhibited specific anosmia towards isovaleric acid.

As in the previous studies, normosmia was ascertained by use of the Sniffin Sticks Identification test (Hummel et al., 2007) in session one, succeeded by assessment of specific anosmia for the respective odors participants had previously been found to exhibit specific anosmia to. No differences between initial testing in study 1 and the retest in study 3 were observed. After initial assessment, an extended "olfactory training" period took place. Participants received smell bottles containing their particular critical odors in 1:10 dilutions, and were instructed to twice daily sniff the odors for 10 s. The training was planned to last at least for four months, but due to time constraints some participants finished training already after two months. In a final session, initial tests for specific anosmia were repeated. The interval between pre- and post-training tests was 63–174 days (mean 99 days, SD ± 31.4).

Improvement of odor thresholds was tested with Wilcoxon Signed Ranks Test for dependent, non-parametric data.

4.2. Results

In the retest in study III, all 25 participants showed improved perception of the respective odors (Fig. 3). None was within the range of specific anosmia after training. We tested whether this result was due to pure chance. By test construction the chance of being classified as normosmic is rather high (.578). Therefore, 15 to 16 out of 25 individuals can be expected to be classified as normosmic by chance. However,

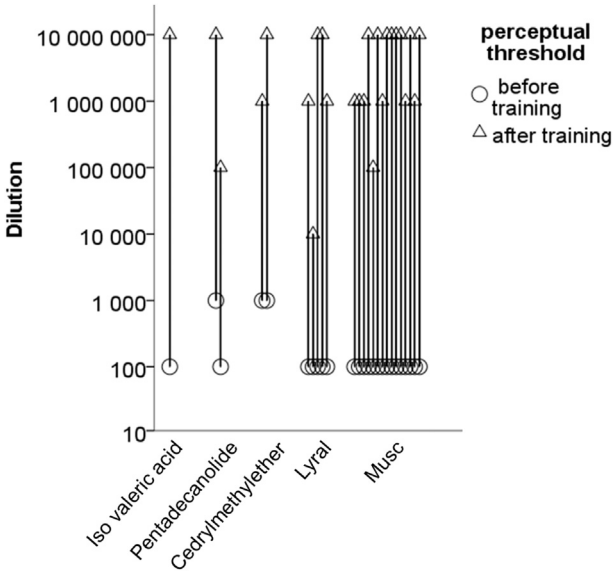

Fig. 3 – Perceptual threshold of people with specific anosmia before and after olfactory training. Lines show individual data of 25 participants that exhibited specific anosmia to isovaleric acid, pentadecanolide, lyral or muscone, respectively. Each of the participants exhibited a strong increase of sensitivity towards the respective odor after training. Accordingly, none of the participants was in the range of specific anosmia after training.

the likelihood of 25 out of 25 candidates to be classified as anosmic is as low as .0001%.

4.2.1. *Conclusion*

Olfactory training improved the participants' perception of the odors above chance.

5. Discussion

The concentration dependent cutoff criterion for specific anosmia resulted in reliable estimation of the rate of specific anosmia per odor, which remained very stable across two different studies. For 18 out of the 20 odors, there was at least one participant with specific anosmia. The molecular weight seems to contribute; odors with high molecular weights were significantly more often associated with specific anosmia. Higher molecular weight may make odors less volatile and may hinder passage through the nasal mucosa. This effect accounted for 24.5% of the variance of specific anosmia.

On an individual level, the probability of being specific anosmic to a particular odor was relatively low, which changed dramatically as soon as more odors were taken into account. The prevalence for specific anosmia to at least one out of 100 odorants approached 1. Surprisingly, this value was strikingly higher compared with previously suggested figures. The approximations estimated from study I were confirmed in study II. Testing 20 odors in each of the participants showed that as many as 34% of the participants exhibited specific anosmia to at least one odor. The probability to exhibit specific anosmia to at least one out of 200 odors was calculated to 99.4% – and there are thousands of different odor-active chemicals (Arctander, 1969). We therefore conclude that specific anosmia is a rule of olfactory perception, not the exception.

This conclusion is based on two assumptions: The rate of specific anosmia to the 20 odors tested here is considered representative for all odorous molecules, and the overlap of specific anosmia between odors is considered representative for all odorants. Our estimation, however, includes some uncertainties. First, although assessing specific anosmia with the method of ascending limits is quick and therefore practical for large scale studies, it is likely to underestimate the rate of specific anosmia. Second, dependencies are not fully taken into account. However, the conservative corrected assumption yielded a 99.5% likelihood of specific anosmia to at least one out of 350 odors, which is still well below the total number of odorous substances.

The most likely explanation why detection of one specific substance may be substantially impaired, while other substances are perceived in the normal threshold range, refers to olfactory receptor expression. Only 49%–82% of the olfactory genes were recently found to be expressed. Moreover, in 26 samples of entire human olfactory mucosa, no evident scheme was found to explain which genes were expressed and which were not. Only 25% of the olfactory receptors were common to all samples (Verbeurgt et al., 2014). However, the reliability of these results is jeopardized by the relatively advanced age of the donors (39–81 years), as an age dependent general decline of the olfactory system is likely. Moreover, the lacking receptors may have been not expressed at all or the degree of expression may have escaped detection. A very low expression rate of some receptors results in peripheral filtering of olfactory information, allowing some odors to reach conscious perception and others to fail.

Such a peripheral filter could reduce the olfactory "noise" and enhance discriminability of the remaining information prior to the stage of the olfactory bulb. A filter mechanism is adaptive if it allows only salient information to pass. We do not know how salient the specific anosmia odors were for our participants. Salience of odors is related to the frequency of exposure to that odor in a meaningful behavioral context. A speculative scenario my illustrate this: Individuals to whom California bay oil is highly relevant in daily life may be less prone to specific anosmia towards its component 1,8 cineole, which contributes 95% of perceived intensity than to the major constituent umbellulone, which contributes only .5% to the percept (Buttery et al., 1974). Rates of specific anosmia to isovaleric acid and musk odor have been shown both to be increased among members of certain families and to vary among human races (Whissell-Buechy & Amoore, 1973). The authors interpreted these results in terms of genetic determinants of specific anosmia. It is, however, equally plausible that the salience of those odors differed with regard to the environmental – be it family or culture related – context.

The highly significant effect of olfactory training in study III is in favor of the peripheral filter theory. All participants with specific anosmia, irrespective of the substance, were well able to detect the respective odors at normal concentrations after the training period. Although some improvement was expected based on pure statistical likelihood, this number strongly implies a training effect. This is in accordance with another study showing that perception of androstenone (another musk odor) can be learned (Van Toller, Kirk-Smith, Wood, Lombard, & Dodd, 1983).

There are at least three alternative explanations of the training effect. **Firstly**, it can be assumed that enhanced perception is due to increased expression of olfactory receptor neurons, and that frequent repetitive stimulation may result in increased expression rates of the relevant receptors. The high turnover rate of olfactory receptor neurons is consistent with the notion of adaptive expression rates. Recently, it has been shown in mice that olfactory learning increases the level of sensory neuron inputs in the olfactory bulb (Abraham, Vincis, Lagier, Rodriguez, & Carleton, 2014). It has been reported that specific anosmia is inherited (Whissel-Buechy & Amoore, 1973), and genetic associations with odor sensitivity support this idea (McRae, Jaeger et al., 2013). It is, however, likely that the expression of olfactory genetic information is in turn shaped by the environment. Most odorous molecules activate more than a single receptor and even in the absence of specific receptors, olfactory detection can be increased by enhanced expression rate of complementary receptors.

Secondly, an alternative plausible explanation of the training effect is that participants' sensitivity to some other receptors affected by the critical odors was improved, either by enhanced receptor expression, by enhanced neurotransmission at those receptors due to learned top down modulation or by modulation at the glomerular level in the olfactory bulb.

Thirdly, participants may have become more sensitized to trigeminal in addition to olfactory compounds of the odors, inducing increased odor detection based on trigeminal input. Even if we believe this to be unlikely at the very low concentrations presented, it ought to be mentioned because detection of trigeminal aspects of odors can also be enhanced by training (Negoias, Aszmann, Croy, & Hummel, 2013).

We conclude that specific anosmia constitutes a peripheral filter mechanism of olfactory perception and impacts on our perception of the world. Besides being not perceived at low concentrations, odors associated with specific anosmia are also perceived as less intense at higher concentrations and they differ in the affective percept. This filter can be trained and consequently allows adaptation to the requirements of the olfactory environment. Further studies on peripheral adaptation of the olfactory system are warranted.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2015.08.018.

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