

Original Article

A Unifying Data-Driven Model of Human Olfactory Pathology Representing Known Etiologies of Dysfunction

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Abstract

In the clinical diagnosis of olfactory function, 2 quantitative extremes of either lost or normal olfactory function are in the focus while no particular attention is directed at the interval between the 2 main diagnoses of “anosmia” or “normosmia”, respectively. We analyzed the modal distribution of olfactory scores with the intention to describe a complex human olfactory pathology in a unifying model. In a cross-sectional retrospective study, olfactory performance scores acquired from 10714 individuals by means of a clinically established psychophysical test were analyzed with respect to their modal distribution by fitting a Gaussian mixture model (GMM) to the data. The probability distribution of all olfactory scores was found to be multimodal. It could be described as a mixture of 6 Gaussian distributions at a high statistical significance level of $P < 10^{-5}$. Moreover, 9 different pathologies associated with the olfactory dysfunction could be shown to be reflected in 1–3 distinct Gaussians. This provides the possibility to assign distinct degrees of olfactory acuity with each etiology. Results indicate that human olfactory pathology is composed of clearly distinct subpathologies that can be connected with underlying subetiologies. We present a unifying data science-based model that satisfies the human olfactory pathology observed in 10714 subjects. The analysis of the distribution of their olfactory performance scores suggests a complex but very distinct human olfactory pathology. This implies a distinction of the olfactory diagnosis of hyposmia from those of anosmia or normosmia.

Key words: bioinformatics, data science, human olfactory pathology, olfactory scores

Introduction

During a person's lifespan, the sense of smell is modulated by various factors such as genetics (Hummel et al. 1991; Zufall et al. 2012), sex (Doty et al. 1985), age (Doty et al. 1984a), environmental damage (Elsner 2001; Snyder et al. 2003), or diseases including neurological maladies. Of these reduced olfaction is an early symptom,

for example, in Parkinson's disease (Doty et al. 1988), Alzheimer's disease (Murphy et al. 1990), or multiple sclerosis (Hawkes 1996), otorhinolaryngological diseases such as head trauma, chronic rhinosinusitis, and viral infections, and their pharmacological treatment (Lötsch et al. 2015). As a result, olfactory function varies among subjects ranging from normal olfactory function up to a complete

loss of olfactory sensations, the latter having an estimated prevalence of approximately 5% in the population (Murphy et al. 2002; Brämerson et al. 2004; Landis et al. 2004; Boesveldt et al. 2011).

In a clinical setting, very often olfactory function is quantitatively assessed. The absence of olfactory function is described as “anosmia”. A strongly decreased olfactory sensitivity is described as “hyposmia” and normal olfactory function as “normosmia”. Typically, the diagnosis of anosmia is based on a test score close to the one that can be obtained by chance. The diagnosis of normosmia is given by scores found in large samples of subjects who indicated an intact sense of smell (Doty et al. 1984b; Hummel et al. 1997). However, no particular attention is directed at the interval between the 2 main diagnoses. Hyposmia is regarded merely as the interval between the 2 score limits. We now report in a study on 10 714 individuals that human olfaction is represented in distinct functional phenotypes. It is not a continuum of scores but clearly multimodally distributed, indicating a complex olfactory pathology that can be associated to the complex etiological causes modulating the human sense of smell.

Methods

Subjects and olfactory testing

This retrospective cross-sectional study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the TU Dresden (number EK251112006). Detailed olfactory test results were analyzed from 10 714 subjects (age: range 6–95 years, mean \pm standard deviation: 52.2 \pm 17 years; sex: 6004 men, 4710 women). Participants had presented at the Smell & Taste Clinic, Dept. of ORL, TU Dresden, with the symptom “olfactory loss”, or had been tested in the context of clinical standard diagnostics (including a standardized history, nasal endoscopy, taste, and smell testing, CT or MR imaging whenever possible/needed) (Welge-Luessen et al. 2013) or were enrolled in research projects as healthy controls recruited via flyers. As suspected causes associated with normal or different degrees of reduced olfactory function were noted: Healthy subjects ($n = 2099$), sinusitis disease ($n = 1637$) congenital ($n = 203$), neurodegenerative diseases ($n = 158$), idiopathic ($n = 1949$), viral ($n = 3053$), head trauma ($n = 1491$), toxic ($n = 90$), and brain tumor/apopleptic insults ($n = 34$).

Following rhinological examination including nasal endoscopy and a detailed structured history (Welge-Luessen et al. 2013), the subjects’ olfactory acuity was quantified by means of the clinically established “Sniffin’ Sticks” test battery [Burghart, Wedel, Germany (Kobal et al. 1996; Hummel et al. 1997)]. This test is based on felt-tip pens that contain solutions of odors instead of liquid dye. The pen’s cap was removed by the experimenter for approximately 3 s and the pen’s tip was placed 1–2 cm in front of the nostrils, in the case of triplet pen presentation at an interval of approximately 3 s. Specifically, odor thresholds were obtained for the rose-like odor phenyl ethyl alcohol presented in 16 successive 1:2 dilution steps starting from a 4% solution. Using a 3-alternative forced-choice task and a staircase paradigm starting at low phenyl ethyl alcohol concentrations, 1 pen with the odorant and 2 blanks were presented at each dilution step. Two successive correct identifications or 1 incorrect identification triggered a reversal of the staircase. The odor threshold was estimated using the mean of the last 4 out of 7 staircase reversals [normal values > 6.0 and > 6.5 for men and women, respectively (Hummel et al. 2007; Croy et al. 2009)]. The odor discrimination was determined with 16 triplets of pens, 2 of each triplet containing the same odor and the third a different, “target” one [for names of

odorants see (Hummel et al. 1997)]. The discrimination performance was assessed employing a 3-alternative forced-choice task (normal score > 10 correct discriminations for both sexes). The odor identification was determined with 16 odors [for names of odors see (Hummel et al. 1997)] using a 4-alternative forced-choice task with presentation of a list of 4 descriptors for each pen (normal score: > 11 correct identifications for males and females) using different stimulus sequences for every measurement. The established evaluation of olfactory performance was based on the calculation of a composite “TDI score” (“Threshold Discrimination Identification”) as the sum of the scores from the 3 subtests (Wolfensberger et al. 2000). Established standard criteria of olfactory diagnosis were indicated by $\text{TDI} \leq 30.5$, with the separation of hyposmia ($30.5 \geq \text{TDI} \geq 15.5$) from functional anosmia, from here termed “anosmia” at $\text{TDI} < 15.5$ (Hummel et al. 2007).

Data analysis

Data were analyzed using the R (version 3.2.1 for Linux; <http://CRAN.R-project.org/>) and Matlab (MathWorks, Natick, MS, USA) software packages. The probability density function (PDF) of the olfactory TDI scores was analyzed using the Pareto density estimation (PDE). The PDE is a kernel density estimator particularly suitable for the discovery of groups in the data (Utsch 2003). PDE was used for density estimation with respect to age and sex of the olfactory TDI sum scores observed in 10 714 subjects (of these 6004 men = 56%). Figure 1 shows the individual TDI scores versus the subject’s age, separately for both sexes and the 9 underlying etiologies. Age dependency was not statistically significant for all etiologies except for the healthy group. Therefore, a sex-specific linear age correction was applied only to the TDI scores of healthy individuals. The individual TDI scores for men were adjusted starting at an age of 34 years with a linear correction of 2.14 per decade of age. The individual TDI scores for women were adjusted starting at an age of 38 with a linear correction of 2.1 per decade of age.

The distribution of the adjusted TDI scores was analyzed using the PDE. This revealed a mixture of different distributions (Figure 2, black line). Subsequently, a mixture of M Gaussian distributions (GMM, i.e., Gaussian mixture model) was used as given by the equation

$$p(x) = \sum_{i=0}^M w_i N(x | \text{Mean}_i, \text{SD}_i) = \sum_{i=1}^M w_i \cdot \frac{1}{\sqrt{2 \cdot \pi \cdot \text{SD}_i}} \cdot e^{-\frac{(x - \text{Mean}_i)^2}{2 \cdot \text{SD}_i^2}} \quad (1)$$

where $N(x | \text{Mean}_i, \text{SD}_i)$ denotes Gaussian probability densities (component, mode) with means, Mean_i and standard deviations, SD_i . The w_i are the mixture weights indicating the relative contribution of each component Gaussian to the overall distribution, which add up to a value of 1. M denotes the number of components in the mixture. GMM fitting was performed with our R package “AdaptGauss” [<https://cran.r-project.org/web/packages/AdaptGauss/index.html>] (Utsch et al. 2015)]. This interactive tool allows to visually adjust the fit, that is, the numerical values could be optimized interactively with the root mean square error between empirical distribution (PDE) and GMM as the fit criterion. To determine the optimum number of components, model optimization was done for $M = 1$ –8 components. The final model was selected on the basis of the Akaike information criterion (Akaike 1974) and visual inspection of the fit. In addition, the Kolmogorov–Smirnov test (Smirnov 1948) was applied to estimate the likelihood that the final model did not adequately describe the data, and the quality of the model to fit the TDI distributions was assessed visually using quantile–quantile plots (QQ plots).

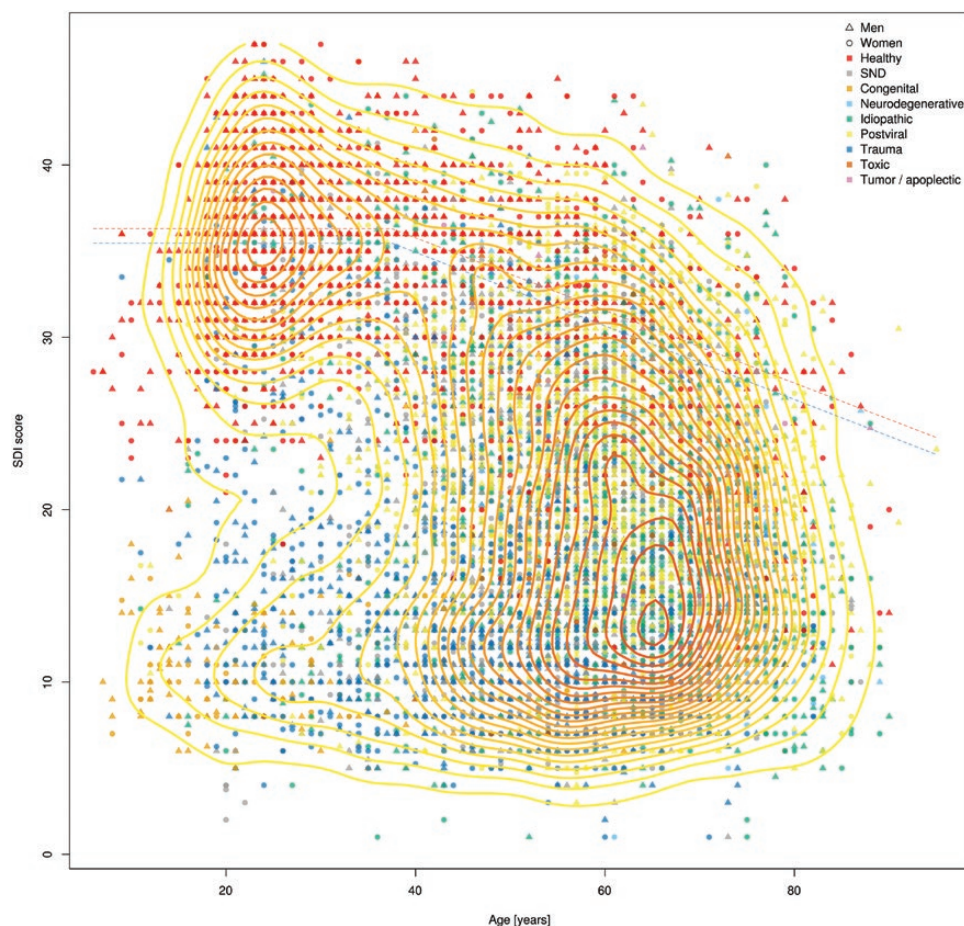


Figure 1. Individual olfactory TDI sum scores observed in 10 714 subjects (6004 men). TDI scores are plotted versus the subjects' age. Separate symbols are used for both sexes and separate colors for the 9 underlying etiologies. The dotplot is overlaid with a contour density plot of the same data. Age dependency of the TDI scores that has been observed only in the healthy subjects aged > 37.5 years is shown as a dotted lines displaying a linear fit.

Finally, the number of Gaussians, among the Gaussians found to describe the general distribution of TDI scores, describing each separate etiology was identified by means of a computed ABC analysis (Ultsch and Lötsch 2015). This is an inventory categorization technique originally developed in economical sciences (Juran 1975; Pareto 1909) to search for the minimum possible effort that gives the maximum yield. It was used presently as a selective inventory category technique that can be used to classify odors into separate categories. The ABC analysis aims at dividing a set of positive data, here the set of weights, w_i , of the Gaussians obtained in the separate fits of each etiology into 3 disjoint subsets called "A", "B", and "C". Subsets "A" and "B" comprise profitable values, that is, "the important few", whereas subset "C" comprises non-profitable values, that is, "the trivial many". The latter can be regarded as not contributing significantly to the distribution and can therefore be neglected. The calculations were done using our R package "ABCanalysis" [<http://cran.r-project.org/web/packages/ABCanalysis/index.html>] (Ultsch and Lötsch 2015)].

Results

Olfactory scores in the 10,714 subjects ranged from 1 to 47, which covered almost the whole possible range of 1 to 48 of the "Sniffin' Sticks" test battery (Hummel et al. 1996; Kobal et al. 1996). Using the established diagnostic criteria of the "Sniffin' Sticks" test battery,

distribution of olfactory diagnoses was 1756 anosmics (37.3 %), 1,853 hyposmics (42.9 %) and 1101 normosmics (23.4 %) in men and 1906 anosmics (31.4 %), 2,575 hyposmics (42.9 %) and 1523 normosmics (25.4 %) in women. The TDI score distribution (Figure 1) differed with respect to the subjects' age. Younger subjects seemed to have either normal or very low olfactory function. Intermediate scores became frequent only at higher ages. A Gaussian mixture analysis indicated that both distribution patterns were best separated (Bayes decision boundary) at an age of 37.5 years.

The distribution of the TDI scores was multimodal as indicated by highly significant results of Hartigan's dip test for unimodality ($D = 0.014479$, $P < 2.2 \times 10^{-16}$). A GMM was applied, which provided a satisfactory fit of the data when using a number of $M = 6$ Gaussians (Figure 2), which was identified by the lowest value in the Akaike information criterion among mixtures using 1 to 8 components. This model described the distribution of the whole set of $n = 10\,714$ TDI scores a high significance level as supported by a $P < 10^{-10}$ in the Kolmogorov–Smirnov test that indicated the probability that the model did not describe the data distribution. This finding was further supported by visual inspection of the respective QQ plots (Supplementary Figure 1). The numerical parameter results of this GMM are shown in Table 1. For the etiological classes with more than $n = 1000$ patients, statistical testing of the empirical distribution versus the respective GMM using Kolmogorov–Smirnov tests obtained always probabilities that the model did not describe

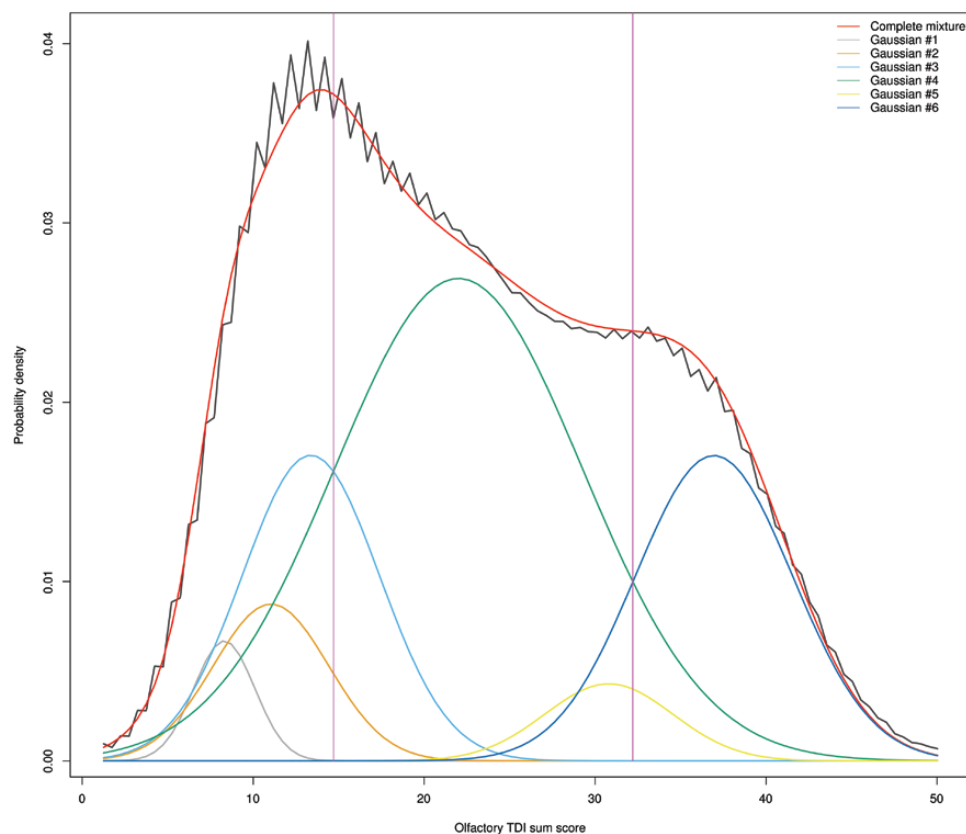


Figure 2. Distribution of the olfactory TDI sum scores observed in 10 714 subjects aged 6–95 years. The density distribution is presented as probability density function (PDF), estimated by means of the Pareto Density Estimation [PDE (Ultsch 2003); black line]. A Gaussian mixture model (Equation 1; GMM given as $p(x) = \sum_{i=0}^M w_i N(x | Mean_i, SD_i)$), was fit (red line) to the data, with a number of mixes of $M = 6$ shown as differently colored lines. The Bayesian boundaries between the 3 largest Gaussians (largest weights) located at TDI = 14.35 and 32. These are indicated as magenta perpendicular lines and roughly reflect the known limits between classical olfactory diagnoses of anosmia, hyposmia, and normosmia. For comparison with a random sample, see Figure 4.

the data of less than 5%. This was visually supported in the respective QQ plots (Supplementary Figure 1).

The 3 major Gaussians in this model were separated at Bayesian decision limits of TDI = 14.35 and 32 between Gaussian 1 and 2 and Gaussian 2 and 3, respectively, that is, close to the standard limits of 15.5 and 30.5 for the separation of anosmia, hyposmia, and normosmia. Additional 3 minor Gaussians were identified. These were needed to satisfactorily describe the whole data distribution. All 6 Gaussians provided a basis to associate the complete human olfactory pathology with underlying etiologies. Specifically, the fit of the TDIs separately for the 9 etiology groups (Figure 3) was possible by only changing the weight factors, w_i , of each Gaussian without changing any value of $Mean_i$ or SD_i (Table 1). Subsequently, the Gaussians which did not importantly contribute to the TDI score distribution of the etiology group, that is, the “trivial many” of the Gaussians”, were eliminated using ABC analysis. This finally provided Gaussians of the ABC groups A and B. This resulted in a number between $M = 1$ and 3 Gaussians for each etiology group (Table 1).

Discussion

Multimodal distribution was observed in the olfactory performance scores of 10 714 subjects. In these subjects, the acuity of their sense of smell was associated with various normal or pathological underlying conditions. This multimodality could be described by a single

unifying model covering the distribution of the whole human olfactory pathology. This includes a clear description of the TDI scores observed in patients in whom olfactory function was reduced due to different currently accepted etiologies of olfactory loss. Subjects were included in this cross-sectional analysis at random with respect to their olfactory function or progression of the underlying disease. Therefore, the consistent multimodal distribution of the TDI scores cannot be resolved by attributing it to the enrolment of subjects at distinct stages of diseases potentially causing olfactory loss. By contrast, it points at a clear qualitative distinction of the human olfactory pathology in separate entities. These include additional olfactory functional entities, in addition to the currently accepted diagnoses of anosmia, hyposmia, and normosmia. The complete unifying model thus sharply contrasts with the present conceptual view of the olfactory pathology as a continuous transition between anosmia and normosmia with a merely quantitative reduction of olfactory function due to various causes.

The study sample was highly selected from the average population as most patients were included who had actively requested medical advice due to perceived olfactory loss, which produced a selection bias toward people who actively reported to a specialized smell and taste unit and possibly, also toward people who lost their sense of smell quickly in order to have become aware of it while a slower deterioration might more pass unnoticed by the patients such as with aging or in Alzheimer’s disease (Nordin et al. 1995; Shu et al. 2009). The sample selection led to a study sample comprising 68% subjects

Table 1. Parameters obtained following modeling of the distribution of the olfactory TDI sum scores by means of a Gaussian mixture model (Equation 1, GMM given as $p(x) = \sum_{k=0}^M w_k N(x | Mean_k, SD_k)$ with a number of mixes of $M = 6$ (Figure 2)

	<i>n</i>	Gaussian					
		#1	#2	#3	#4	#5	#6
All subjects, complete GMM							
<i>Mean_i</i>	10 714	8.31	11.04	13.37	22.01	30.80	36.95
<i>SD_i</i>		1.78	3.38	4.01	7.24	3.74	4.59
<i>w_i</i>		0.03	0.07	0.17	0.49	0.04	0.2
GMM weights (<i>w_i</i>) for separate etiologies							
Healthy	2099	0	0	0	0	0.05	0.95
Sinunasal disease	1637	0	0.31	0.04	0.59	0.04	0.02
Congenital	203	0.41	0	0.52	0	0	0.07
Neurodegenerative	158	0	0.27	0	0.73	0	0
Idiopathic	1949	0.01	0.09	0.38	0.41	0.05	0.05
Viral	3053	0	0	0.08	0.92	0	0
Head trauma	1491	0.1	0.27	0.25	0.38	0	0
Toxic	90	0.04	0.13	0.23	0.44	0	0.23
Tumor/apoplectic	34	0	0.65	0	0	0.23	0.11

Mean, SD, and *w_i* are the parameters mean, standard deviation, and relative weight of each of the Gaussians, respectively. At the top part, the general model of human olfaction is represented with its parameter values. At the lower part, the weights of the 6 Gaussians observed for the 9 etiologies are shown. All human olfactory pathology can be represented by this model by adapting the respective weights. The 3 main Gaussians, that is, novel olfactory subpathologies, associated with each etiology of olfactory (dys-)function after eliminating noise parts are given in bold letters and shaded table cells.

with reduced olfactory function contrasting to the normal prevalence of olfactory dysfunction of 18% in a random sample of the average population (Vennemann et al. 2008), which may increase with age (Murphy et al. 2002). Importantly, while this selection influenced the apparent prevalence of olfactory dysfunction, it played no causal role in the reported modality in the distribution of the olfactory scores, the selection only made the observation of the already present modes possible which in a random sample might have included too few patients to become statistically detectable. This was verified in the following informatics experiment (Figure 4). In a 100-fold repeated experiment, samples comprising $n = 820$ (82%) healthy subjects and $n = 180$ (18%) subjects with olfactory dysfunction were drawn randomly from the original data. This provided a distribution that agreed with that observed in an unselected population sample (Vennemann et al. 2008). The present GMM could be adapted to each of the empirical distributions at $P < 0.01$, which provides a proof for the suitability of the GMM to model the present data. The experiment was repeated with the differences that this time, to the $n = 820$ (82%) randomly selected healthy subjects we added $n = 180$ (18%) data drawn from a uniform distribution. For this distribution, the best adaptation of the GMM achieved in 100 repeated experiments a $P > 0.7$. Hence, if the modality would not have been present, a selection of the subjects could not have arbitrarily produced it, which shows that the present observation of multimodal distribution of olfactory scores is not a result of the selected study cohort. Finally, a multimodal distribution was found to be also present in the single components of the olfactory sum score, that is, in the distributions of odor threshold, odor discrimination and odor identification (see Supplementary Figure 2). This supports the validity of the present results and indicates that the reported multimodality of olfactory scores is not a solitary finding with a particular sum score but will probably prevail under modified olfactory test conditions such as a different number of olfactory subtests. There is also no immediate reason to doubt that the present results would have been analogously found with other olfactory tests [for an overview, see (Rombaux et al. 2009)]; however, proof cannot be provided from the present data.

The present evidence indicates that all olfactory pathology is multimodal and that different etiologies can be captured, with respect to their associated TDI scores, by combinations of multiple Gaussian distributions. The evidence implies that human olfactory pathology is complex and that the current etiological classification is overly simple; it fails to recognize subetiologies of larger categories. For example, a distinction into 2 major subgroups was found for the olfactory function of patients assigned to a congenital lack of olfaction. This was defined based on the patients' medical history who could not recall any perception of odors throughout their lives. From the present analysis of 203 of such patients, it emerged that this pathology is divided into 2 subgroups comprising either subjects with absent or subjects with residual olfactory function. This well corresponds to a genetic concept of congenital olfactory loss in which the TDI score distribution reflects the typical pattern for a gene dose effect. It argues for the idea that an additive model of heredity applies and homozygous carriers of a causal mutation would be anosmic and expected to appear in the first Gaussian (Figure 3), while heterozygous carriers with residual olfactory function, that is, hyposmia, would be expected in the second Gaussian.

A multimodal distribution was also observed in the olfactory TDI scores acquired from patients who had sought ENT support because they attributed a loss of their sense of smell to the exposure to toxic substances. A few of them had normal olfactory function according to the standard diagnostic criteria of the Sniffin' Sticks test which was reflected in the appearance of a separate Gaussian at the right side of the distribution. These subjects might have feared olfactory damage or their claims might have been motivated by a desire for compensation without a pathological basis. However, the TDI scores of the patients in this etiological subgroup who had less-than-normal olfactory function were bimodally distributed. Different degrees of reduced sense of smell could have been a consequence of different doses of the toxic or of different toxics that reduce the olfactory function to either anosmia or hyposmia.

A multimodality in the distribution of olfactory functional scores prevailed in most subgroups of subjects regardless of the underlying

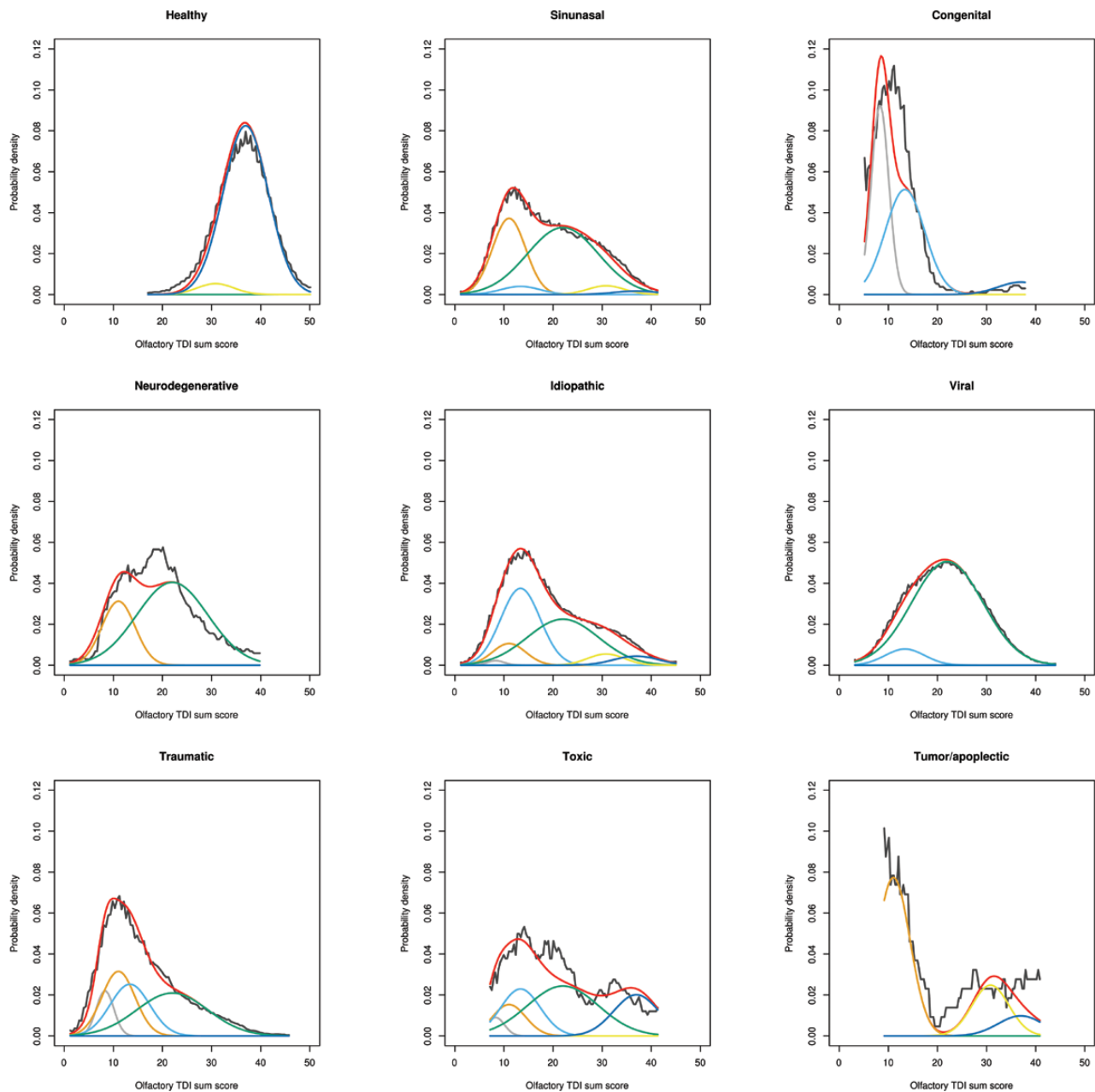


Figure 3. Distributions of olfactory TDI sum scores, separated for etiologies. The density distribution is presented as probability density function (PDF), estimated by means of the Pareto Density Estimation [PDE (Ulltsch 2003); black line]. A Gaussian mixture model (Equation 1; GMM given as $p(x) = \sum_{i=0}^M w_i N(x | Mean_i, SD_i)$), was fit (blue line) to the data with a number of mixes of $M = 6$ (color coded as in Figure 2). The distributions are described by a single model; with a particular combination of weights w_i (Table 1) it is possible to represent all the specific distributions for each diagnostic subgroup.

etiology of the olfactory dysfunction, except for the healthy subjects who were, as expected, mostly normosmic. A pronounced subgroup structure in patients with tumors or apoplectic insults can be considered as attributable to different localization of the lesion. Similarly, the unimodality of olfactory dysfunction observed after a viral infection corresponds to the clinical perception that this disease is a sole entity associated with decreased but still residual olfactory function.

The distinction into subgroups in patients in whom an olfactory loss was attributed to a neurodegenerative disease appeared to be less well fitted by the single model of human olfactory function (Figure 3). This can be easily attributed to the pooling of TDI scores for both sexes while this etiology appears with sex-differentiated

frequencies. Indeed, a sex-specific separate analysis of the data provided a better fit (not shown) indicating that the apparently poorer fit was due to neglect of this confounder.

Olfactory dysfunction is an early symptom of neurological diseases such as Parkinson's disease (Doty et al. 1988), Alzheimer's disease (Murphy et al. 1990), or multiple sclerosis (Hawkes 1996). However, patients were enrolled at any stages of their neurodegenerative diseases. The observed multimodal distribution of the olfactory scores fits better to a stratification of neurodegenerative diseases for the induced degrees of olfactory dysfunctions into causes of either anosmia or hyposmia. Such an interpretation would be supported, for instance, by claims that olfactory tests can discriminate

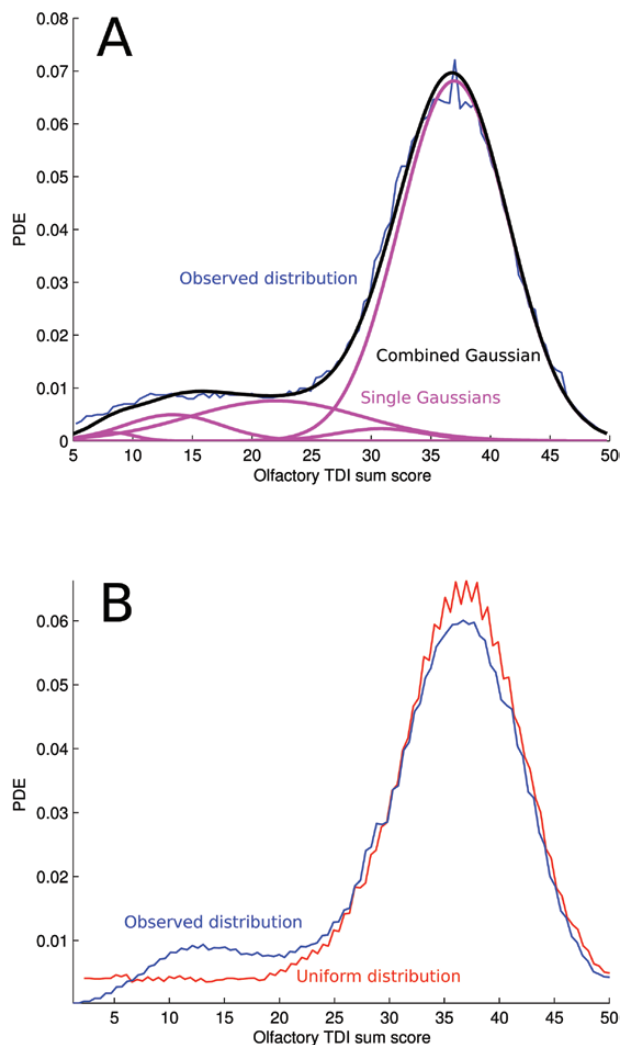


Figure 4. Bioinformatics experiment demonstrating that the present multimodality was not a result of the inclusion of a selected study sample. (A) shows the adaptation of the multimodal GMM to data containing TDI scores from 82 % subjects with normal olfactory function and 18 % subjects with reduced olfactory function randomly drawn from the original data, which corresponds to the prevalence of normal or reduced olfactory function in a random sample of an average population (Vennemann et al. 2008). (B) shows how the distribution would appear if the underlying sample were not multimodal but merely uniformly distributed whereas in the scenario displayed in (A), the present Gaussian mixture model could be adapted to each of the empirical distributions at $P < 0.01$, the GMM was rejected at a $P > 0.7$ for the scenario in (B). Hence, the multimodality was not introduced by the selection of subjects in the clinical setting but describes an empirical distribution valid for a random sample drawn from a population.

Alzheimer's dementia from other forms of dementia (Duff et al. 2002) or from major depression (McCaffrey et al. 2000).

In this article, we show that the human olfactory pathology is composed of clearly distinct subpathologies that can be connected with underlying subetiologies. We present a general model that satisfies the human olfactory pathology observed in 10 714 subjects. The analysis of the distribution of their olfactory performance scores suggests a complex but very distinct olfactory pathology, implying a distinction of the olfactory diagnosis of hyposmia from those of anosmia or normosmia. It indicates that human olfactory function is not simply gradually reduced related to duration and intensity of

the action of various factors that can deteriorate it. By contrast, the results point at the effects of different etiological causes that can lead to distinct olfactory diagnoses. This suggests a revision of current concepts of human olfactory pathology with regard to hyposmia. It replaces the concept with a more complex idea that is consistent with the complexity of etiological causes of olfactory dysfunction. This has probably also prognostic implications.

Supplementary material

Supplementary material can be found at <http://www.chemse.oxfordjournals.org/>

Author contributions

J.L. conceived and designed the analysis; J.L. and A.U. analyzed the data; J.L. wrote the paper and T.H. provided data.

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Conflict of interest statement

The authors have declared that no competing interests exist.

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